AUDITORY EVOKED POTENTIALS IN CHILDREN WITH COCHLEAR IMPLANTS: A PRELIMINARY STUDY

by

Emily Jo Venskytis

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This thesis was presented

by

Emily Venskytis

It was defended on

April 10, 2013

and approved by

David Chi, MD, Otolaryngology, School of Medicine

Phillip Gilley, PhD, Speech, Language, & Hearing Sciences, UC Boulder

Sheila Pratt, PhD, Communication Science and Disorders, SHRS

Barbara Vento, PhD, Communication Science and Disorders, SHRS

Thesis Director: Deborah Moncrieff, PhD, Communication Science and Disorders, SHRS

LATE CORTICAL AUDITORY EVOKED RESPONSES IN COCHLEAR IMPLANTS: A PRELIMINARY STUDY

Emily Venskytis

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This is a preliminary and exploratory study designed to investigate the use of electrophysiologic recordings of cortical auditory evoked potentials (CAEPs) as an objective test measure for patients who have a cochlear implant (CI), with a more specific goal of learning best practices for extracting the CI artifact from the collected data. The particular evoked potential of interest was the P1-N1-P2 complex. It was hypothesized that normal latencies and peak amplitudes of the late-evoked potential (P1-N1-P2) would reveal characteristics that may correlate with behavioral data to indicate the level of benefit with a cochlear implant. The study included three participants, each with one cochlear implant on the right side: two males, age 13, and one female, age 10. The study also evaluated electrophysiologic data from two normal-hearing volunteers, age 21. Data was collected via a 64-channel electrode cap with two reference electrodes placed on the mastoid and two additional upper and lower vertical eye channels. The stimulus was created using the guidelines by Dimitrijevic et al. (2008, 2011) and consisted of two test blocks of 250 Hz and 4000 Hz, respectively, with frequency modulations at 0% (no change), 2%, 4%, 10%, 25%, and 50% every 1.4s, lasting for approximately 100ms. Evoked potentials were recorded in response. The ongoing EEG was decimated and converted into MATLAB® format to run an independent component analysis (ICA) using the runica algorithm (Bell & Sejnowski, 1995). A method of waveform extraction was developed in MATLAB® and EEGLAB in order to evaluate the peak amplitudes and latencies.

Following ICA, independent components presumably affected by the cochlear implant were identified and rejected according to methods adapted from Gilley et al. (2006). Data was highly variable across the small number of subjects, raising several questions about age at implantation, length of CI use, etiology of hearing loss and speech/language processing abilities in the pediatric user. From this study, it appears that the artifactual component from the implant can be removed from the electrophysiologic response so that CAEPs in children with CIs can be investigated across a larger number of individuals from this pediatric population.

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PREFACE

I am thankful to many people who helped me or offered support during this research process. Below is a short list of the people that I wish to thank that contributed to the completion of this thesis.

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1.0 INTRODUCTION

A cochlear implant (CI) provides direct electrical stimulation to the auditory nerve and is typically used for severe to profound sensorineural hearing loss (SNHL). It allows for the perception of sound. Benefits of this device vary widely depending on numerous factors, which has been a point of research for many years as the CI has developed. According to the American Speech-Language Hearing Association (ASHA), more than 36,000 people have received the implant (American Speech-Language Hearing Association, 2004). In addition, a CI is now available to children as young as 12 months of age. Candidacy for the implant requires a detailed process of evaluation, even though the restrictions are lessening with continued research and discoveries.

The implant has been in use for about two decades, and has undergone substantial changes as the technology has improved. The focus of research has been transitioning from determining the viability and safety of the implant towards new measures of implant success and reasons for those varying levels in implanted children. Since there are many co-occurring disorders with SNHL, for example, Auditory Neuropathy Spectrum Disorder (ANSD), and different symptoms that fall under the same diagnosis, the success of the CI varies. This inconsistency is the reason that one person would not do as well with a CI as another. Due to the varying levels of success, the primary goal of this study is to explore the use of objective measures for determining whether a CI recipient is having positive progress with their implant

and to see if this type of measure can further provide insight into the underlying pathology that other tests have been unable to clarify. The aim of this study is to collect electrophysiological results and compare them to behavioral reports in children with a CI. The overall objective of this study is to determine if electrophysiological measures could be used to predict results on behavioral measures following implantation, and to see which objective measures are related to greater implant success. If objective measures are found to be useful in this way, electrophysiological results could be used to gauge success immediately following and possibly even prior to implantation.

This is a preliminary and exploratory study to investigate the usefulness of electrophysiologic testing for children with CIs. There are a multitude of reasons that electrophysiologic testing should be investigated for clinical use as an objective measure with cochlear implantation, discussed in Section 1.2. The possibilities for co-occurring disorders and unknown difficulties are vast due to the intricacies of the auditory system. Electrophysiologic testing may help to provide a better measure of performance than typical behavioral tests. It is hypothesized that behavioral and electrophysiological tests will be correlated because increased synchrony of the auditory nerve reflected as latencies of the P1-N1-P2 complex presenting at normal levels should occur in children with better performance on behavioral measures of comprehension. This test measure should therefore be a good determinant of increased synchrony after implantation compared with no change. Theoretically, the findings could indicate that this test has potential to be used to predict success in children pre-implant, allowing electrophysiologic testing to provide a measure that increases cost-effectiveness as well as enhances reliability of implantation. At the least, this study will further confirm that the

collection and analysis of the P1-N1-P2 response is a viable means of objective testing post-implant in children.

1.1 COCHLEAR IMPLANTS

The initial plan of this study was to investigate those who have received a CI who have ANSD. Due to dys-synchronous neural firing and general difficulty with a CI, discussed in the next section, these patients are a good test population. Although connections were made with Dr. David Chi of the Hearing Center of the Children's Hospital of Pittsburgh, there was difficulty in acquiring participants. The information regarding ANSD and an implant has been deemed still relevant and useful, because it is possible for dys-synchrony and general difficulty with a CI without the diagnosis of ANSD. The following sections give a general background on ANSD and CIs, candidacy for a CI, and levels of performance post-implant.

1.1.1 Auditory Neuropathy and Cochlear Implants

Since the term Auditory Neuropathy (AN) was coined by Starr et al. in 1996, the disorder's definition has developed and progressed to include many factors. It is unclear as to how many patients have this disorder due to misdiagnosis, the wide range of pathologies potentially associated with the disorder, and differing test populations. The highest figure produced by research is that 10%-15% of patients with SNHL have this disorder (Sharma et al., 2011), but it may in fact be less than 1%. Since the coining of the term, Auditory Neuropathy has been called many names, including Auditory Dys-Synchrony and Pre-Synaptic Sensorineural hearing loss.

The most recent, and the name that will be used in this paper, is Auditory Neuropathy Spectrum Disorder (ANSD). This is because exact site of the lesion and pathology is not known, and it is probable that varying disorders of temporal processing or deficiencies within the auditory system may be causing similar test results. A diagnosis of ANSD is made following the initial test result of absent or abnormal auditory brainstem response (ABR) despite the presence of otoacoustic emissions (OAE) and/or cochlear microphonics (CM) (Kumar & Jayaram, 2006; Marco et al., 2000; Rance & Barker, 2009; Sininger & Troutwein, 2002). Presence of OAEs/OMs indicates the outer hair cell must be functioning but either the inner hair cells or the ascending pathway function is impaired (Hayes, 2011). The results of tests are not always static, and patients with ANSD may have varying functioning of the auditory system over time, which complicates diagnosis (Sininger, 2011). OAEs may even disappear in about half of the patients who have been diagnosed with the disorder. Although this causes hearing perception difficulties, the patient with ANSD may not have a large degree of hearing loss—it ranges from mild to profound. The degree of hearing loss is not necessarily related to the main symptom of the disease, meaning that the underlying pathologies of the SNHL and ANSD can be different.

Even though these basic features that determine ANSD can be measured audiologically, the primary difficulty with the diagnosis and treatment of the disorder is that symptoms are inconsistent and unpredictable. There are a multitude of locations of lesion and causes that have been described as contributing to the symptoms of ANSD including absent or disordered inner hair cells, irregular function of synapses at inner hair cells, or a loss of synchrony because of demyelination (Sharma et al., 2011; Zeng & Liu, 2006). Some have written that because ANSD may be a spectrum of differing locations and disorders, patients can be found who have speech perception performance that correlates with their hearing loss and others who comprehend

speech signals more poorly than expected based on their hearing thresholds; which means that even if there are very good pure tone hearing thresholds, the patient still may be unable to differentiate between speech signals and noise (Kumar & Jayaram, 2005; Sininger & Troutwein, 2002). Because of this disproportionality, it has been noted that the ability to discern and comprehend speech does not depend on hearing within levels necessary to comprehend speech but on the way the signals are processed within the pathway (Kumar & Jayaram, 2005). The discrimination and decoding of speech signals has been found to be particularly challenging in situations where there is background noise, with speech in quiet being easier to comprehend. One theory is that there is a range of results with ANSD patients in part due to differences in "their ability to use temporal cues" (Berlin et al. 2010). Kumar & Jayaram (2006) further this by noting that in ANSD, one theory is that the neuron or receptor cells have an inability to phase-lock. When this occurs, the speech signal is being sent at different times, possibly distorting it or making its way through as an incomplete portion of the requisite neural code. This causes general difficulty in speech perception, and would support the idea that speech-in-noise is even more difficult for many patients with ANSD.

Since it is not known exactly where the neuropathy occurs, either for the individual patient or in general for the disorder, management varies. More recently, as CIs have become more popular, patients with ANSD and hearing loss ranging from moderate to profound levels have been receiving a CI as treatment (Jeong et al. 2007; Rance & Barker, 2009; Sininger & Trautwein, 2002). If acquisition of language and ability to orally communicate is shown to be extremely dysfunctional, despite less severe degrees of hearing loss, patients who have ANSD have been implanted once they have shown no success with conventional amplification. It has been proposed that if the lesion is at the level of the inner hair cells, causing dys-synchronous

neural firing, the CI may create better synchronization. If the lesion is along the VIIIth auditory nerve or somewhere else along the pathway, the patient may not do as well.

Although dys-synchrony is the main problem in patients who have ANSD, there may also be patients who are not diagnosed with ANSD but have a degree of dys-synchrony present with their SNHL. Speech-in-noise and determining the location of lesion is also a difficulty with general implantation without the presence of ANSD. One can look to the problem with ANSD as a glimpse into what may be causing those problems with speech-in-noise and other general difficulties in CI recipients who have SNHL. There is research that suggests that a CI synchronizes the signal in reaction to an auditory stimulus, and there have been many children who have received a CI with ANSD and synchrony has been achieved (Rance & Barker, 2009). Because of the unknowns within the auditory system, developing more tests that can evaluate the location of the problem and the usefulness of the implant would be beneficial to determine outcomes and potentially predict outcomes. Since receiving a CI requires a serious surgical procedure, there is an abundance of tests prior to the determination that a person is a good candidate for a CI, discussed in the next section. Although these tests have been developed and are very detailed, improvement could be made in the research and knowledge about how the CI can create such a change in some but not in others.

1.1.2 Candidacy, Behavioral Testing, and Implant Outcomes

In order to receive a CI, an individual's candidacy is intricately evaluated. Assessment for candidacy is multi-disciplinary with many factors involved. Starting with degree of hearing loss and lack of success with other means of amplification, such as a hearing aid, other criteria are: age, cognitive development, physical health, and psychological and environmental factors

(Niparko & Blankenhorn, 2003). One test that is used pre- and post- implant is the Meaningful Auditory Integration Scale (MAIS), a test specifically targeted towards infants and young children (Niparko & Blankenhorn, 2003; Sharma et al., 2011). The MAIS is a questionnaire that evaluates the patient based on the parent or guardian's perspective. The questions pertain to the amplification device, bonding to device, reaction to auditory stimuli, and the way the patient incorporates these auditory stimuli. The scores are then placed in categories from Bronze to Gold. Additional tests include, but are not limited to, exploring residual hearing, means of communication, level of verbal communication, and educational placement.

Despite the extensive tests and preparation before implantation, it is not possible to definitively know the level of success the patient will have with the implant, or even if the device will succeed at all. For this reason, many studies have been performed on patients post-implant not only to see how well people can do with them, but also as retrospective studies to determine which factors may serve as the best predictors of ultimate success with the CI (van Dijk et al., 1999; Wie et al., 2007). Co-occurring disorders have been known to further complicate predicting success as they can also affect CI performance and have more unpredictable results.

The long evaluation process before determining candidacy for a CI is an attempt to maximize success with implantation. Success with cochlear implantation, although generally good, is variable and does not always occur even in children with SNHL without co-occurring disorders as well as with ANSD (Hyde et al., 2010; Jeong et al., 2007; Niparko & Blankenhorn, 2003; Rance & Barker, 2009). Prior to implantation, it is important to realize that there are factors that can influence success before the patient even undergoes the surgery. One of those factors is the patient's age. This can create varying results in patients with CIs because, although it has been changing, some will not have been determined to be a good candidate for a CI until a

few years into their life. A reason this can affect how well the person does with the implant is due to the potential for a sensitive period for the development of the central auditory system. These hypotheses are discussed in Section 1.2.1, below.

There are many other general factors that can influence success with the implant. Wie and colleagues (2007) found that the factor that most influenced performance in speech recognition and comprehension was daily CI use. The other factors which influenced speech recognition then follow from most influential to least: non-verbal intelligence, mode of communication, length of time post-implant, and last being the educational setting. Those that used the CI the most and had an oral education were also typically in mainstream education. Time of CI experience is also most likely not a highly contributing factor because amount of time since implantation does not matter if it is not used on a regular basis. Speech-recognition growth rate was determined by Wie and collaborators (2007) to be fastest in users who were youngest at the time they received the implant, had shortest experience with the implant, were born deaf, and spent most of their education time in mainstream education. Early use of a hearing aid before implantation seems to create a more positive outcome on speech recognition.

Other ways to investigate the success of the implant would be to evaluate the phonological accuracy and word production of the implantee (Ertmer & Goffman, 2011; Wie et al., 2007). Many studies evaluated performance in these areas using outcome measures which include the Speech Intelligibility Rating, where speech and language therapists specializing in working with deaf children rated the speech intelligibility of the children under review using six categories (Edwards et al., 2006). Word production and intelligibility should be considered outcome measures of importance due to language development being related to hearing capabilities and processing of sound cues to learn production. In other words, if they are

producing the correct sounds, in the absence of therapy, then they are likely hearing those sounds correctly.

The Children's Hospital of Pittsburgh in particular uses a few main tests during implant follow-up appointments as regular behavioral measures of outcomes post-CI. Speech awareness is tested, along with speech recognition thresholds using spondee words. The Lexical Neighborhood Test (LNT) and Multisyllabic Lexical Neighborhood Test (MLNT) are also often used. Both of these tests are open-set tests of speech perception, making them more difficult and therefore more reliable for judging speech understanding than closed-set tests with response choices (Kirk et al., 1995). The test is performed in the free sound field from speakers, also relating it to everyday experience. The LNT only contains words with one syllable, whereas the MLNT follows the same principle, but has words with more than one syllable. These tests are based on the idea that word knowledge is related to the word's "neighborhood", which contains words that differ from the target word by only one phoneme (Greenberg & Jenkins, 1964). When the target is not frequent in daily use and has more words within its neighborhood that occur frequently in speech production, it is classified as denser and therefore more difficult to recognize (Luce, 1986, 1990). The MLNT has been found to be easier for patients with a CI due to the smaller neighborhood of multisyllabic words as well as the additional cues that are provided by the length and number of syllables of the word (Kirk et al., 1995). Both the LNT and the MLNT have "easy" and "hard" lists organized by the determined difficulty of the word based on its lexical neighborhood. Kirk and colleagues (1995) hypothesized that these tests are able to measure more sensitive changes in word recognition throughout time. The MLNT and LNT are therefore a useful means of evaluation of CI recipients (children) as they develop language skills.

Speech-in-noise is another area that needs to be evaluated in children who receive a CI. Noise is present in many situations, and it is often an area that needs attention in aural rehabilitation and classroom and social settings. Often, the difficulty with speech in noise is due to the capacity of the CI itself, with limited channels as compared to the thousands of hair cells used during acoustic hearing (Caldwell & Nittrouer, 2013). The ability to understand the speech signal and recognize it against background noise also depends upon the person's own knowledge of their language and its structure. This is impacted by how long the person has had their implant and its effectiveness, so that they were able to learn their native language. Beyond this, there are other problems at the level of the cochlea and along the pathway, such as dys-synchronies, demyelination, and pathways that have not matured, which can affect the ability to understand speech-in-noise.

If a child is implanted, parental perspective can be used both for determining implant success and for retrospective studies to see how they could have prepared the family more or been able to better predict the implantee's results. Parent perspective is not only important to see how well the child is doing, but also to see if their expectations for post-CI meet the outcomes they have experienced for their child—to see if they find the treatment cost-effective (Hyde et al., 2010). The parent perspective, along with the range of results and outcomes after implantation, are the reasons behind further research in the retrospective view, to determine tests that may better predict what the outcome may be before the implant is received. Better measures of determining success pre-operatively, found through relation of results to tests post-operatively, can prepare parents and implantees so their anticipated benefits can coincide more with their received outcomes. Hyde and colleagues (2010) investigated the relation between the preoperative perspective of the parent and the parent's reaction to the received outcome. They

noted “The parent of a child now 7 years old wrote, ‘I was expecting the implant to “fix” his hearing as I had seen children with implants talking and hearing beautifully. As [our child] has Auditory Neuropathy he has scrambled hearing and only a vocab of about 6 words” (Hyde et al. 2010). It is problems like this and the cases of poor results with implantation discussed earlier that prove implant measures need to be investigated further. More recent studies and discussion about ANSD stress the importance that the clinician and parent realize the child may not have the desired benefits from their CI, or the degree of improvement from baseline may be minimal, but at this point it is very difficult to predict results pre-implant once typical determinants are factored out (Hayes 2011). This can be applied when any patient undergoes surgery for a CI, regardless of etiology.

It is very important for the clinician to adequately prepare the patient and family for unfavorable outcomes prior to undergoing surgery for a CI. In the section *Patient Counseling and Expectations* in ASHA’s practice policy regarding CIs, ASHA encourages “redundantly reviewing the range of performance, including the bottom of the range” in order to give reliable expectations (American Speech-Language Hearing Association, 2004). As discussed above, there are many factors that affect CI benefits, so there are a variety of outcomes. The policy is in place because there have been both great successes and more unfavorable results. Parents always anticipate the great successes, but need to be prepared for a different achievement level than they would optimally desire.

Although there are many clinical tests and determining factors that influence implant success, it is important to determine which are most relevant to the everyday life of the patient. The relationship between parental perceptions of development and outcome measures has been investigated to determine which best reflects a child’s abilities in the home setting as noticed by

the parent. It has been noted in the literature that parent reports are almost as important as clinical tests, but clinical tests can also be relevant to the home situation (Lin et al., 2008). There were certain tests that Lin and colleagues used to compare and contrast and they can be found in Table 1.

Table 1: Measures of Success with the Implant

Test	Description
MacArthur Communicative Development Inventory-Words and Gestures	A parent-recorded measure of language ability for 8- to 16-month olds
Reynell Developmental Language Scales	Clinician-administered test of a child's language abilities in a clinical environment
Early Speech Perception Tests (ESP)	A closed set that examines pattern perception, spondaic word identification, and monosyllabic word identification using toy objects to represent the stimulus items
Meaningful Auditory Integration Scale (MAIS)	Evaluates the patient based on the parent or guardian's perspective using questions which pertain to the amplification device, bonding to device, reaction to auditory stimuli, and the way the patient incorporates these auditory stimuli
Visual Analog Scale (VAS-development)	Caretakers draw their own line on a chart to represent their realization of the child's progression in the past month as it relates to communication with others and expression of thoughts

After comparing the parental responses with clinical measures, the authors came to the conclusion that the MacArthur and the Reynell produced highly comparable results (Lin et al., 2008). This signifies that the Reynell, although a clinical report, can be used to relate to the home setting and relates to everyday life for the child, as the parent perceives it. Knowing which tests are most relevant to everyday situations can be especially helpful for patients, since clinical tests are often speech-in-quiet and patients with difficulty in-noise may excel in optimal conditions. Another study, which tested how patients with ANSD performed with speech-in-noise, concluded that the CI does seem to help improve ANSD performance, but they found that it did not entirely remove the difficulties of hearing in-noise, meaning it does not eliminate difficulty with speech-in-noise for many other CI recipients (Zeng & Liu, 2006). It appeared that the

majority of good results were found with tests of speech-in-quiet. This means that even with the CI, performance in all areas is not perfect and does not necessarily improve abilities in the main area where these patients have the most difficulties and it is important to use relevant clinical tests. In the current study, one goal is to see if electrophysiology is a useful and viable objective measure that correlates to daily use of the implant in all settings.

1.2 CORTICAL AUDITORY EVOKED POTENTIALS (CAEPS)

An evoked potential is a reaction at the level of the neurons within the nervous system. The Auditory Evoked Potential (AEP) is exogenous, which implies that it is in response to a sensory stimulus (Burkard et al., 2007; McPherson, 1996). The AEP is also an automatic response, meaning it can be objectively recorded via electrophysiologic collection of waveforms. This is a great advantage to behavioral testing and patient surveys in the field of audiology. There are a variety of AEPs that occur at different times post stimulus, all of which can be recorded using an electrode cap. The P1-N1-P2 complex is a late-latency, obligatory, and passive AEP that has been used in studies with subjects who have ANSD and subjects who have CIs, making it applicable to evaluate the status of synchrony and maturation in the cortical response in a patient post-implant (Dimitrijevic et al., 2011; Dorman et al., 2007; Sharma et al., 2007). This is the response that has the longest latency of the AEPs, and each peak will be discussed in detail below (McPherson, 1996). Attention is not a factor in the collection of this waveform and the person does not have to attend to the stimulus for the exogenous response to occur, as long as they are able to hear it.

The P1, N1, and P2 responses are often investigated as a whole due to their contingent relationship (Burkard et al., 2007; McPherson, 1996). The collection of these responses produces a waveform with the P1 and P2 defined as positive peaks and the N1 as the negative peak in between them (See Figure 1 for an example image of a typical manifestation of the P1-N1-P2 Complex). Presence of this complex indicates that the sound signal has reached the auditory cortex and that it has potential for discrimination by the auditory cortex (Burkard et al., 2007, p. 484). The P1-N1-P2 complex has been said to be "highly sensitive to disorders affecting the central processing of sound" and that it is often used "to index changes in neural processing with hearing loss and aural rehabilitation; and to identify underlying biological processing disorders in people with impaired speech understanding" (p. 495). The measurements of the waveform (latencies and amplitudes) are comparable to normal-hearing individuals in those with CIs who have had positive results and differ in patients with CIs who have lower performance, according to Burkard et al. (p. 494). This implies that this test correlates with behavioral results in implant users. The N1, in particular, has a later maturation and investigation of this peak may imply a matured auditory system, as discussed in Section 1.2.1.1 (Eggermont & Ponton, 2002). This study will compare the latencies and peaks with normative data as well as with behavioral test scores to see if in fact these measures can correlate and if this measure can be used reliably post-implant as an objective evaluation. Figure 1, from McPherson (1996, p.78) shows the typical manifestation of the P1-N1-P1 complex (P60, N100, N160, respectively) as well as their typical measurement.

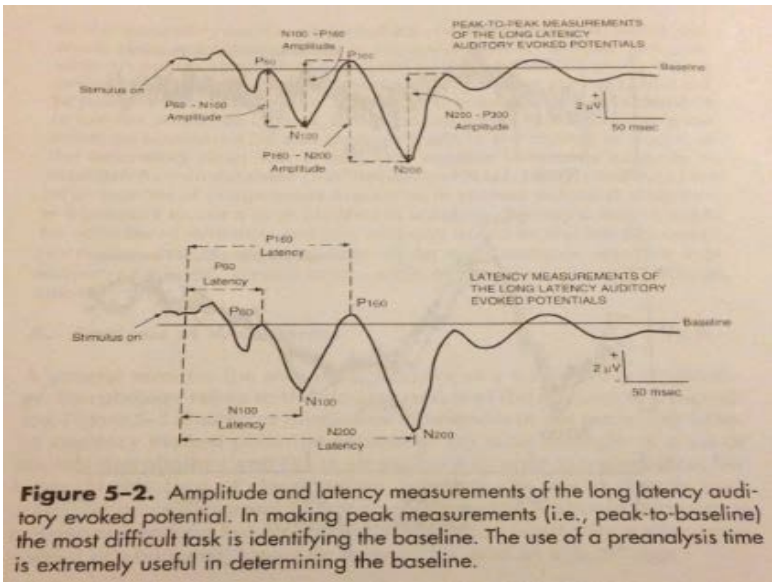


Figure 5–2. Amplitude and latency measurements of the long latency auditory evoked potential. In making peak measurements (i.e., peak-to-baseline) the most difficult task is identifying the baseline. The use of a preanalysis time is extremely useful in determining the baseline.

Figure 1: Typical P1-N1-P2 Manifestation

Each peak can be interpreted individually because each peak is thought to relate to different capabilities of the auditory system. Latency information is available for each peak, but amplitude information is variable and depends on numerous factors, such as the stimulus. Typically, P1 has been said to correlate with the behavioral outcome on the IT-MAIS, so it is possible that the others can correlate and give more information about the pathway (Sharma et al., 2011). The P1 latency occurs typically between 55ms and 80ms in adults (McPherson, 1996). Children who have ANSD often produce a delayed or missing P1 response (Sharma et al., 2011). The P1, therefore, reflects problems with synchrony due to the signal arriving at varying times subsequently creating an averaged peak that is delayed, abnormal, or absent (Sharma et al. 2011; Starr et al., 2001). This would imply, then, that if someone with a CI does not have appropriate synchrony, this will be seen in the latency and amplitude of the P1. Sharma and colleagues (2011) conclude that although the dys-synchrony affects the P1 amplitude, it does not appear that ANSD affects cortical maturation as much because the P1 was often still present, even if its morphology was abnormal. A dys-synchrony will create problems with speech-in-noise, so the

P1 response could potentially be an objective measure of how well a patient's speech understanding is in noise conditions, an important factor in everyday hearing.

The N1 is a negative peak with a latency that occurs typically between 80ms and 150ms in adults (McPherson, 1996). The N1 is thought to index the awareness of a difference or additional sound in the ongoing sound signal or background noise (Eggermont & Ponton, 2002). The N1 is discussed in more detail in Section 1.2.1.1. The P2 is a positive peak that occurs at a latency between 145ms and 180ms (McPherson, 1996). The P2 is related to the perception of the auditory stimulus, but there is not much information related to the P2 as its own entity. It is often considered as a group with either the N1 alone or the P1 and N1 together. The latencies of the responses are all affected by cortical maturation, and this is discussed in the next section.

1.2.1 Auditory Cortical Maturation

Auditory cortical maturation has been a large focus of research throughout recent years. It has been explored primarily through the use of Cortical Auditory Evoked Potentials (CAEPs). There are two primary figures in the literature on cortical maturation that will be discussed in this section. The two have differing views on auditory cortical maturation and have formatted their research as such. Eggermont supports the theory that maturation occurs at any age based on the amount of time in sound for the P1 and P2, but there is a cutoff for the development of the N1. Sharma supports the theory of a critical period for auditory maturation of P1, N1, and P2 and places focus on the P1. This section is not meant to exclude any major researchers and emphasizes the main authors on the literature as a brief background in cortical maturation as the reasoning behind the current study, evaluating CI success and the justification for limiting the study to children over five years of age. This research dialogue is one from a few years prior to

the formulation of this study. Figure 2, from McPherson (1996, p.95), is a representation of the typical maturation pattern of the late evoked potentials.

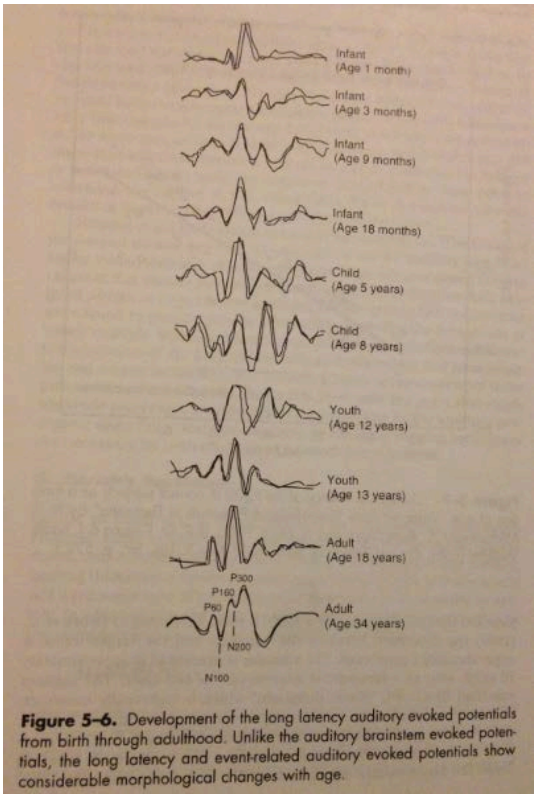


Figure 5–6. Development of the long latency auditory evoked potentials from birth through adulthood. Unlike the auditory brainstem evoked potentials, the long latency and event-related auditory evoked potentials show considerable morphological changes with age.

Figure 2: Maturation of the late CAEPs

1.2.1.1 Eggermont on Maturation

Eggermont, individually and in collaboration with Ponton, has devoted much time to researching cortical activity, maturation, and responses to sound. He has investigated the auditory cortical system in humans along with cats, monkeys, and other animals. This section serves to summarize his findings and ideas in relation to Auditory Evoked Potentials (AEPs), mismatched negativity, and cortical maturation in regards to the human auditory system, particularly in children who receive CIs. He has used electrophysiological testing to evaluate changes in the auditory system development due to maturation (Ponton et al., 1996). A large focus of Eggermont and his colleagues has been to contribute to the discourse about whether there is a cutoff for pathway

development or if, when stimulation begins again via cochlear implantation, maturation continues along its typical path because of retained plasticity.

The perspective that Eggermont has maintained throughout the research is that there is no sensitive or critical period for the majority of the auditory system's maturation, although development of the auditory system after deprivation may not progress in the exact likeness of a child with no hearing deficits. In 1996, Ponton and colleagues determined that "the maturation of P1 latency progresses at the same rate but is delayed in implanted children by approximately the period of deafness" (p. 62). They concluded, "Time-in-sound, defined as chronological age minus the duration of deafness, is the appropriate independent variable to study these maturational changes" (p. 64). This means that there is normal development if you consider the time in-sound for the child who has received a CI in place of where you would consider chronological age for a normal-hearing child.

Eggermont, Ponton, and others also spent time describing and defining the different latencies of Auditory-Evoked Potentials (AEPs) and aspects of other electrophysiological test measures. This often included analyzing the P1-N1-P2 complex. The authors label these as late cortical responses (Eggermont & Ponton, 2002). Of particular interest to them is the N1 peak. These articles support the hypothesis that the N1 peak is a reflection of a perception of a change in a part of the "auditory environment" and may in fact reflect a change in focus or "attention switching" (p. 75). It is possible then that this peak would signify the ability of a person to discriminate the presence of the sound or a change in the presence of a sound.

Maturation of the brain does not occur all at once, rather there are different periods and ages at which maturation and development begins and ends. This can be seen explicitly through the late-latency AEPs. Maturation of the P1 and P2 are typically completed by the time the child

is five years old, but the N1 continues to change for many years following (Eggermont & Ponton, 2003; Ponton et al., 2000). Because of this, the maturation of the N1, which is a negative peak, has an impact on the P1 (which matures earlier and can be recorded earlier). Ponton and colleagues noted, "as N1 becomes increasingly more negative, P1 decreases in amplitude" (2000, p. 176). As N1 increases, P1 decreases, thus making it necessary to examine the P1 and N1 together in the current study due to the ages of the participants. For the purposes of evaluation of the magnitudes of the peaks, one should expect to see a relationship between the two amplitudes: if the N1 is smaller than average, the P1 should be larger. In addition, Eggermont and colleagues contest that the N1 does not appear in recordings before around 7 years of age. What contributes to this is that the N1 peak is more likely a representation of superficial layers of neurons—which have been said to mature later, rather than the other components (such as P1) that lie deeper. Through determining maturational phases, N1 and structural maturation has been related to development of "perception of speech in noise" and "degraded speech", which have corresponding time frames (Eggermont & Ponton, 2003, p. 250). Since the N1 matures later in normal-hearing individuals, it is possible that a robust N1 in a patient with a CI would imply that the patient's auditory system has matured post-implant to be able to discriminate those more complex sounds.

Using this information, on AEPs and electrophysiology results, the researchers have continued to evaluate development of the auditory system after deprivation of sound followed by re-introduction to sound. Using P1 latency, Eggermont et al. have furthered support for their hypothesis that it is not the chronological age of the child that should impact the development of deaf implanted children, but instead it is their "time-in-sound"; they noticed that the values of latencies with this considered, "fitted perfectly with the age-dependent hearing values"

(Eggermont & Ponton, 2003). This continues to support the idea introduced above that plasticity remains, at least for the area that creates the P1 latency, and resumes maturation once stimulation to the auditory system resumes.

After further investigation and longitudinal studies examining neuroplasticity of the auditory system, they noticed that even counting "hearing age", N1 latency did not occur at the time it was expected to—it was either absent or abnormal (Ponton & Eggermont, 2003). This information together implies that P1 and P2 may be developed with weak stimulation or without auditory stimulation altogether but the N1 (being a representation of more superficial layers rather than deep) needs stimulation and does appear to have a critical period, which means it probably does not retain its plasticity. The absence of the development of N1 also coincides with the results that two implanted children who developed P1 but did not develop normal N1 latencies had normal scores on speech in quiet tests but were unable to discriminate speech sounds, or did much worse; again supporting that N1 reflects discrimination of speech in noise (Ponton & Eggermont, 2003). An interesting point to note, is that the researchers included in their hypothesis that it may not only be plasticity which causes the P1 and P2 to resume normally, but that a high powered hearing aid before implantation may be enough to keep the brain active as to facilitate maturation.

1.2.1.2 Sharma on Maturation

Sharma, Dorman, Gilley, and their collaborators have also performed extensive work in the areas of CAEPs with implantation and especially in regards to maturation. Following is a short summary of some of the articles written by this cohort.

The main proposal in Eggermont's work is that the maturation of the P1 and the P2 does not depend on a critical period, but instead is either autonomous or needs very minimal

stimulation to mature at normal rates. They do agree that the research suggests that the N1 has a critical period. There is another opinion in the body of research that differs slightly from the former's perspective. In this research fronted by Sharma, Dorman, and Gilley, there is the theory that all of the late evoked potentials (P1-N1-P2) are affected by maturation and have a cut-off age for maturation to be able to occur normally. This would have great implications upon research with CAEPs, and it is important to consider these opinions and recognize the age of the implantees in addition to their time in-implant.

Sharma and colleagues have performed numerous experiments, with a primary focus on the P1, that determine that there is a critical period for the cortical areas of the auditory system that correspond to the P1, N1, and P2 (Gilley et al., 2008; Sharma et al., 2002, 2009). Since the latencies decrease for these potentials during cortical maturations (primarily in the first ten years of life), a delayed latency, especially for the P1, would imply that the auditory system is immature (McPherson, 1996, p. 90; Sharma et al. 2002). This cohort hypothesizes that a child who is implanted during the "sensitive period" will then perform and develop the best post-operatively because for maturation to occur, there must be auditory stimulation (Sharma et al., 2009). This is because of plasticity and reorganization in the brain, which occurs with presence or lack of stimuli. For this reason, and based on studies evaluating the latency of the P1 in participants who have received a CI, Sharma and colleagues have concluded that there is a critical period of about 3.5 years for auditory cortical maturation in relation to the P1 (Dorman et al., 2007; Gilley et al., 2008; Sharma et al., 2002, 2009). If the person receives a CI within their first 3.5 years, then the P1 will still reach a normal latency. If it is between 3.5 and 7 years it is more likely, and after 7 years the latency has been seen to be more abnormal. This information has implications on any study that evaluates the late evoked potentials and each subject and age

of implantation must be considered during electrophysiologic testing. It is interesting to note that this body of work focuses almost entirely on the P1, while the former places a central focus on the N1.

1.2.2 Stimulus Use

The P1-N1-P2 complex has different response and latency data for the different aural stimuli that are presented. One type of aural stimuli that is often used is the presentation of a pure tone and modulations to that tone. For the purpose of this study, frequency modulations to two different pure tones are presented in two separate test blocks via a loudspeaker; see the Methods section for information regarding the creation of this stimulus. The original creation and use of this stimulus was with the purpose of assessing participants diagnosed with Auditory Neuropathy Spectrum Disorder (ANSD). Since this stimulus was used as a tool for investigating the CAEPs of these patients with dys-synchronies, it was fitting that although the participants in the current study do not have ANSD, the stimulus was still evaluated as an objective measure of testing of participants who have received a CI. This stimulus can be used to test the synchrony and sound discrimination in these patients as it did with patients who have ANSD.

1.2.3 Cochlear Implant Artifact

Recording the CAEPs involves using electrodes that pick up signals emitted from the scalp. Since the CI is an electronic device, it also emits a signal picked up by these electrodes during the collection of the data. One of the largest challenges with the use of electrophysiologic testing to evaluate a patient while they are using their CI in free sound field is in the removal of the

artifact created by the electrical energy of the implant. The primary goal of this study was to learn the methodology for extracting the artifact produced by a CI during the recording of a cortical evoked potential in children. Gilley uses the infomax approach by way of the runica algorithm (Bell & Sejnowski, 1995; Gilley et al., 2006). This approach uses the MATLAB® software (2012, The MathWorks, Natick, MA) with the EEGLAB toolbox and ERPLAB plug-in (Delorme & Makeig, 2004; Luck & Lopez-Calderon, 2012). The EEGLAB toolbox allows the user to perform an Independent Component Analysis (ICA) on the continuous or epoched data once the file is imported into MATLAB (Delorme & Makeig, 2004). ICA is more beneficial than PCA for the purposes of this study because it allows the user to reject components that are entirely separate from each other, rather than PCA which creates components that are created subsequently from each component prior (Gilley et al., 2006). The artifact creates a pattern within individual components that can be identified in the waveform and is shown in Figure 3 (from Gilley et al., 2006). The ERPLAB plug-in is an important addition to the EEGLAB toolbox in that it can further process the data in order to average epochs separately within the data according to type numbers that are pre-programmed into the stimulus (Luck & Lopez-Calderon, 2012).

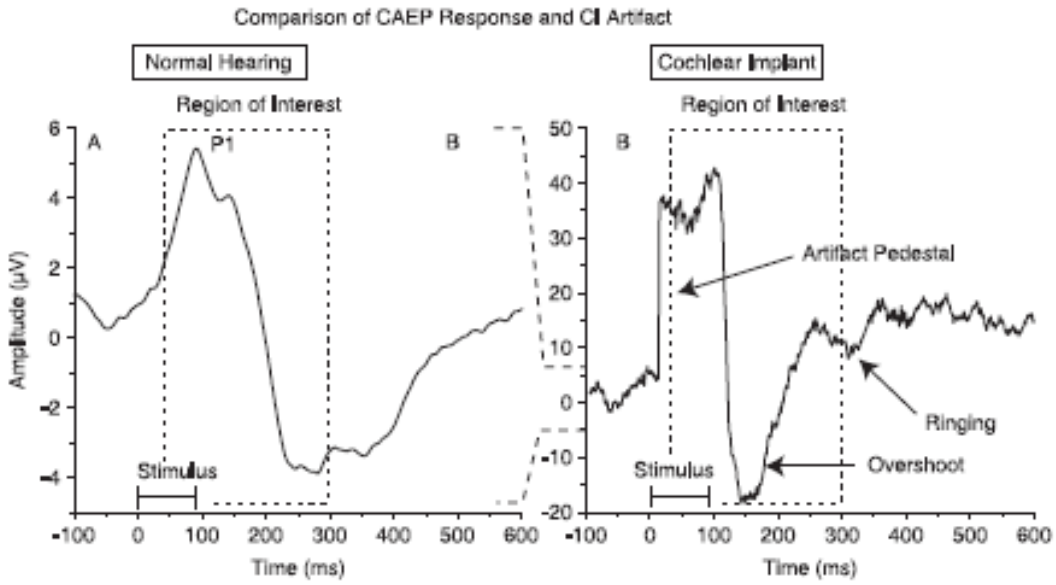


Figure 3: Artifact Pedestal

After separating the data into independent components, each component can be examined for its scalp distribution, CAEP response waveform, and distribution of power (Gilley et al., 2006). The means for determining if an independent component is due to a CI artifact are discussed in Section 2.3.

2.0 METHODS

This study uses the stimulus parameters created by Dimitrijevic, described here (Dimitrijevic et al., 2008, 2011). The stimulus uses two different test blocks that have base frequencies of 250 Hz and 4000 Hz, respectively. Every 1.4s, there is a frequency modulation lasting for approximately 100ms. These frequency modulations are at 0% (no change), 2%, 4%, 10%, 25%, and 50% above the base frequency. For example, the 250 Hz tone will play for 1400ms and a 255 Hz tone will play in addition to and simultaneously with the base for the next 100ms. This is the 2% modulation. When the modulation frequency is at exactly 100ms, there is an occasional occurrence of non-integer cycles. To correct this and to minimize the audible change caused by a non-integer cycle, some of the modulations are slightly longer, creating as close to an even number of cycles as possible. A 5% Blackman window was also added to each pure tone modulation. The base and modulation stimuli were created using Neuroscan Stim2© Sound and were compiled into a randomized test block with each modulation type occurring 100 times using Stim2© Gentask software. The base of 250 Hz or 4000 Hz, respectively, runs throughout the entire test block as a background parameter. The ITI for each modulation is 1400ms. A rationale for using this type of stimulus when recording the CAEP in children with cochlear implants stems from research indicating that implanted individuals process speech signals more for their envelope characteristics and less for the temporal fine structure typically used by individuals using normal auditory processes (Lorenzi et al., 2006).

2.1 PARTICIPANT RECRUITMENT AND DEMOGRAPHICS

Following a full board review by the University of Pittsburgh's Institutional Review Board, potential participants were identified via collaboration with the head audiologist at the DePaul School for Hearing and Speech as well as with the director of the Hearing Center at Children's Hospital of Pittsburgh. These professionals work closely with the prospective subjects and are known to the parents. Participants considered for this study were those with a unilateral CI between the ages of 5 and 16. If participants were known to be uncooperative, they were not invited to participate. The professionals sent the approved letter home to the parents along with the consent document. Parents reviewed the consent forms at home and called the investigator after reading the consent document so that the study could be described and any questions answered.

During this phone conversation, the principle investigator explained the study to the parent using the script in Appendix A. If after this conversation the parent was willing to allow their child to participate, an appointment was made. Potential subjects were reminded that participation is voluntary and were told that they may change their minds regarding participation at any time. At the time of the study, each child was asked to provide assent.

Three participants agreed to partake in the study, all of which were recruited from the Children's Hospital of Pittsburgh. As shown in Table 2, two of the participants were age 13 and one was 10. The ten-year-old is a left-handed female currently in a total-communication school setting who was implanted at age 4 with a Freedom Contour Advance device but is currently using a Nucleus processor in the right ear and a hearing aid in the left ear. Both of the 13 year olds are right-handed males, with Nucleus 24 implants in their right ears. One of the thirteen-year-olds received his implant less than 5 months prior to testing and wears a hearing aid in his

left ear. The other thirteen-year-old received his implant at age 26 months and has a hearing aid, but does not frequently wear it.

Table 2: Patient Demographics

Subject	Age (yrs)	Age at CI	Time in-CI	Type of CI	Gender	Handedness
S1	13	12 years	5 mo.	Nucleus CI 512	Male	Right
S2	10	4 years	6 years	Freedom Contour Advance, Nucleus Processor	Female	Left
S3	13	26 mo.	11 years	Nucleus 24	Male	Right

2.2 CAEP TESTING

Following the signature of the consent document and question period at the appointment, the subject was seated in a chair for the application of the cap. The Neuroscan SynAmp2© system was used for testing subjects. This computer system connects to an electrode cap, the Neuroscan Quik-Cap© shown in Figure 4, which has 64 active electrodes (Ag, AgCl, sintered) plus 2 linked reference electrodes, placed on the right and left mastoid. To eliminate contamination by eye muscle activity, the researchers used two additional channels, 1 upper and 1 lower vertical channel that was used via VEOG with artifact rejection described in Section 2.3. This is necessary because when the eyes move, it may create action potentials that interfere with the desired collected waveforms at frontal electrode sites. Therefore, the electrodes above and below the eye collect information and allow for removal of the response for those times that there was contamination from eye movement.

Figure 4 Neurscan Quik-Cap, Compumedics

The cap was placed on the child's head and checked for correct size. It was insured that the cap was tightly fitted but was not too tight on the child's head. For conduction, each electrode was filled with Quik-Gel, a salt-based conducting gel, and all impedances were established at <10 megaOhms. The electrodes directly above where the CI is connected to the head were not filled with gel so that the CI was not damaged during testing. Therefore, fewer than 64 electrodes were established in connection with the head. Once impedances in all active electrodes was affirmed, testing began.

Data from two normal-hearing young-adult subjects was collected by the same methods in order to evaluate the peaks and latencies in comparison to the CI population data. Normal-hearing subject 1 (NH1) was tested with the full electrode array. NH2 was tested with only a cross section of electrodes (Cz lines).

2.2.1 Presentation of the Stimulus

Subjects were seated in a sound-attenuated room in a comfortable chair. They were told that they did not have to do anything except sit in their seats and were allowed to play games on their personal game device or tablet. In order to examine cortical functioning in the most natural situation, two of the children wore their hearing aid, because they typically used it during the day (S1 and S2). The other child (S3) elected to not wear his hearing aid. The child was asked if he/she was ready to begin. The stimulus was presented via a loudspeaker at 0 degrees azimuth at a distance of 0.8 meters. The 250 Hz signal was presented at 58 dB SPL (measured using C-weight scale on a sound level meter). The 4000 Hz signal was presented at 54 dB SPL (measured using C-weight scale on a sound level meter). Each test block took approximately 14 minutes and between the two test blocks, subjects were able to stand up and stretch and take a 3-minute break. The total appointment lasted approximately 1.5 hours.

2.3 WAVEFORM EXTRACTION

Data collection resulted in a Neuroscan continuous file. The continuous file contained all EEG data from the onset of the block to its termination. A checklist used for each subject that includes all of the steps for waveform extraction can be found in Appendix B. First, the continuous file was opened, and bad or inactive electrodes were marked and subsequently removed. A form of principle component analysis (PCA) was then performed on the file in order to find one component that accounts for a high degree of variance representing the eye blinks, which were then filtered out of the data. The steps for this PCA can be found in the top line of Appendix B.

The sampling rate was then reduced to 1000 Hz via the decimate function in Scan Edit in order to import the file into MATLAB/EEGLAB. There is an incident of redundant events common to Neuroscan continuous files, not matching the number of stimuli, which was then corrected using a batch .tcl file. Upon the correction of this error, the decimated continuous file was imported into EEGLAB, using the file-io format. In EEGLAB, an event file was created with data imported from a Neuroscan .ev2 file that contained epoch information and channel location data was imported via the default setup.

In ERPLAB, a new event file was created in order to translate Neuroscan's trigger-labeled events into bins that group the recording by trigger type. Bin-based epochs were then extracted. Following epoching, an ICA was run with the runica algorithm in EEGLAB (Bell & Sejnowski, 1995; Gilley et al., 2007). The criteria for rejection was developed based on the methods by Gilley and colleagues (2007) but due to the use of different stimuli in this study, new criteria needed to be established. All independent components were identified first by examining the headplots of all of the components for a positive polarity centered in the area of the implant. The waveforms of components with positive polarity in the area of the implant were then visually examined for excessive noise. This noise was either throughout the entire duration, due to the background signal, or during the duration of the stimulus modulation. If the excessive noise occurred during the stimulus, the waveform was evaluated for similarities to the artifact pedestal identified in Gilley et al., 2007, see Figure 3. In addition, data that occurred in a similar

distribution manifestation as the artifact but contained a negative peak at around 100ms was retained in the data as to not affect the measurement of the N1[1].

The final epoched data was post-hoc filtered through a low-pass filter of 30 Hz. The average waveform for each stimulus type following the rejection of the artifact was then computed in ERPLAB. The latency of each peak response, their amplitudes, and the peak-to-peak amplitude were all measured and recorded. Although baseline correction was performed, some of the waveforms did not line up precisely with the baseline (0). The amplitude of each peak was also collected in relation to the relative baseline, individually for each average. The same process, with the exclusion of the ICA process, was used to analyze the data from the normal-hearing participants.

2.4 BEHAVIORAL INFORMATION

The three participants were recruited from Children's Hospital of Pittsburgh. Each participant's results on behavioral scores and audiologic records were collected from the Children's Hospital

[1] The primary component of interest is in relation to the CI. In addition to these components, there was an incidence of components containing a large positive response around 300ms. These components were most likely a reflection of a cognitive response caused by allowing the participant to play a game during testing. Since the latency of these components occurred later than the latencies of interest for analysis, the components were retained in the data.

of Pittsburgh upon presentation of the signed consent form. This data is available in the Results section.

3.0 RESULTS

In order to be concise, this paper only reports the findings on the CI artifact rejection process and the responses to modulations at 25% and 50% of each base frequency (250 Hz and 4000 Hz), measured at Cz. These modulations were chosen because they have been shown to demonstrate the maximum response to frequency-modulated auditory signals (Dimitrijevic et al., 2011).

3.1 ARTIFACT REJECTION

CI artifact rejection could be performed using the MATLAB EEGLAB toolbox Independent Component Analysis (ICA). The components that were rejected, along with a sample of components that were considered for rejection but were retained, can be found in Appendix C. Components that were rejected were also evaluated for their statistics: including variance, range, skew-ness, and excess kurtosis. There did not appear to be a trend with the statistics of the rejected components, except that they were all super-Gaussian. These component statistics can also be found in Appendix C. It was verified that the resulting waveform, post-rejection, differed from the original waveform for each data file. This evidence can be found in Appendix D.

Since the participants were allowed to play a game on a device or tablet, there was a large frontal component present in some of the data. In the independent components, these often manifested near a latency of 300ms, which would affect the P3 but presumably not the earlier

components. As to not affect the desired response, these components were retained in the data. Figure 5 has an image of Subject 2 (S2) at 4000 Hz with a 25% modulation. The large P3 could possibly be attributed to the game playing and attention.

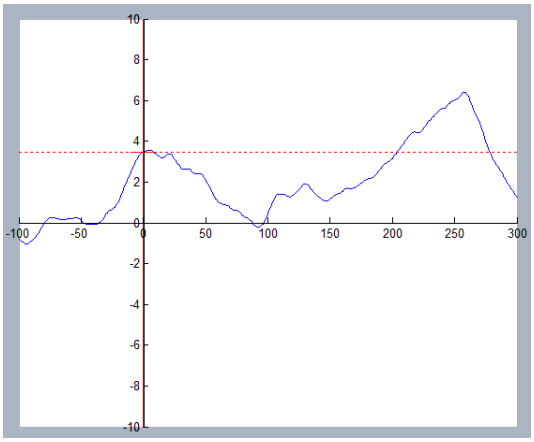


Figure 5: Large P3 Component

3.2 P1-N1-P2 RESULTS

P1-N1-P2 measurements varied for each participant at the Cz electrode. Table 3 supplies information on whether or not each peak was detected at each frequency modulation (25%, 50%) of each base (250 Hz, 4000 Hz), as well as the peak-to-peak amplitude of P1-N1. The peaks were measured between certain values based on latency data provided by McPherson (1996) and based on the latency range used for the N1 by Dimitrijevic et al. (2011), unless a very obvious peak close to the range was identified. P1 was evaluated between 50ms and 100ms. N1 was evaluated between 80ms and 180ms. P2 was identified at the first positive peak after the N1. If there was no peak within the latency range, the data were marked in Table 3 as N for 'no peak'. This may indicate that the peak was absent, but it can also indicate a delayed peak or abnormal

peak that was unable to be identified. The precise peak and latency measurements for each subject at each modulation (25%, 50%) of the base (250 Hz-top, 4000 Hz-bottom) are in Table 4. This table also has the values for the manually corrected peak measurements to baseline and the peak-to-peak amplitude of P1 to N1. In Table 4, if there was no peak within the norm time window, the space was marked as "unclear", to indicate the possibility for an abnormal, absent, or delayed peak.

Table 3: Presence of Peaks

Subject:	FM	P1	N1	P1-N1	P2	Subject:	FM	P1	N1	P1-N1	P2
250 Hz						4000 Hz					
S1	25	Y	Y	0.90	Y	S1	25	Y	Y	3.02	Y
S1	50	Y	Y	0.38	Y	S1	50	Y	Y	0.10	Y
S2	25	Y	Y	0.93	N	S2	25	N	?	-	Y
S2	50	Y	N	-	Y	S2	50	N	Y	-	Y
S3	25	Y	Y	0.93	N	S3	25	Y	Y	0.18	N
S3	50	Y	Y	1.61	Y	S3	50	Y	Y	2.05	Y
NH1	25	Y	Y	2.99	Y	NH1	25	Y	Y	3.05	Y
NH1	50	Y	Y	3.89	Y	NH1	50	Y	Y	2.68	Y
NH2	25	Y	Y	2.20	Y	NH2	25	N	Y	-	Y
NH2	50	Y	Y	3.95	Y	NH2	50	Y	Y	1.00	Y

Table 4: Peak and Latency Measurements

250 Hz						
Subject	Wave Baseline	Peak Label	Peak	Latency	Peak with base corr.	Peak-to-peak (P1 to N1)
S1_250 at 25%	0.17	P1	-0.50	65.37	-0.67	
		N1	-1.40	87.82	-1.57	0.9
		P2	-0.38 or 0.88	153.98 or 222.47	-.55 or .71	
S1_250 at 50%	0.33	P1	-0.03	95.12	-0.36	
		N1	-0.41	108.59	-0.74	0.38
		P2	0.65	139.95	0.32	
S2_250 at 25%	0.77	P1	0.16	106.13	-0.61	
		N1	-0.77	129.38	-1.54	0.93
		P2	unclear	unclear	unclear	
S2_250 at 50%	0.26	P1	2.60	86.52	2.34	
		N1	unclear	unclear	unclear	unclear
		P2	2.18	141.54	1.92	
S3_250 at 25%	0.27	P1	1.49	83.77	1.22	
		N1	-0.12	115.73	-0.39	1.61
		P2	0.44	144.13	0.17	
S3_250 at 50%	0.93	P1	0.17	125.11	0.76	
		N1	-1.44	147.00	-2.37	1.61
		P2	1.67 or 1.80	180.37 or 210.87	0.74 or 0.87	
NH1_250 25%	-0.86	P1	0.73	64.76	1.59	
		N1	-2.26	129.63	-1.4	2.99
		P2	-1.40	174.95	-0.54	
NH1_250 50%	-0.37	P1	1.08	81.04	1.45	
		N1	-2.81	120.57	-2.44	3.89
		P2	0.50	200.37	0.87	
NH2_250 at 25%	0.55	P1	1.01	66.49	0.46	
		N1	-1.19	95.11	-1.74	2.20
		P2	-0.99	110.85	-1.54	
NH2_250 at 50%	-0.27	P1	0.04	89.68	0.31	
		N1	-3.91	132.52	-3.64	3.95
		P2	-3.11	162.54	-2.84	

4000 Hz						
Subject	Wave Baseline	Peak Label	Peak	Latency	Peak with base corr.	Peak-to-peak (P1 to N1)
S1_4000 at 25%	0.19	P1	1.20	82.15	1.39	
		N1	-1.82	176.60	-2.01	3.02
		P2	-1.60	190.33	-1.79	
S1_4000 at 50%	0.41	P1	0.85	95.75	0.44	
		N1	0.75	110.48	0.34	0.10
		P2	1.30	123.31	0.89	
S2_4000 at 25%	3.47	P1	unclear	unclear	unclear	
		N1	?? -0.22	?? 92.39	?? 3.25	unclear
		P2	1.90	130.02	-1.57	
S2_4000 at 50%	0.03	P1	unclear	unclear	unclear	
		N1	-7.11	137.22	-7.14	unclear
		P2	-2.19	239.95	-2.22	
S3_4000 at 25%	-2.18	P1	0.28	96.11	2.46	
		N1	0.10	102.82	2.28	0.18
		P2	unclear	unclear	unclear	
S3_4000 at 50%	-0.47	P1	0.084	53.66	0.554	
		N1	-1.97	79.92	-1.5	2.05
		P2	0.57	109.93	1.04	
NH1_4000 25%	-0.80	P1	0.39	68.71	1.19	
		N1	-2.66	125.66	-1.86	3.05
		P2	-1.23	158.95	-0.43	
NH1_4000 50%	-0.12	P1	-0.13	85.98	0.01	
		N1	-2.81	120.69	-2.93	2.68
		P2	0.5	200.37	0.62	
NH2_4000 at 25%	0.39	P1	unclear	unclear	unclear	
		N1	-2.17	151.97	-2.56	unclear
		P2	-1.46	204.59	-1.88	
NH2_4000 at 50%	0.59	P1	0.66	88.42	0.07	
		N1	-0.34	136.47	-0.93	1.00
		P2	unclear	unclear	unclear	

In the data for the CI participants (S1, S2, S3), modulations on 250 Hz and 4000 Hz produced different levels of response, with the 4000 Hz base having a more robust change. There was a noticeable difference in the waveforms between the 25% and 50% modulations of the same base frequency in most of the subjects. This can be seen in Figure 6, providing the response of S2 at a 250 Hz base with both 25%(left) and 50%(right) modulations. In all of the following images, the red line indicates the adjusted baseline.

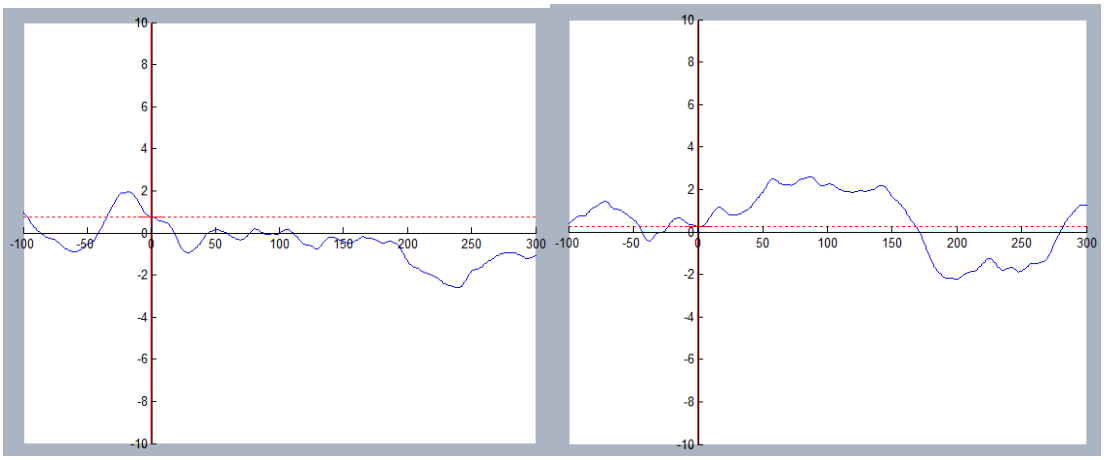


Figure 6: Difference between 2 frequency modulations of the same base

Information from the two normal-hearing volunteers is also in Table 4 (NH1, NH2). These volunteers have normal hearing and did display an expected response in the test conditions, indicating that the method of waveform extraction was able to produce a viable waveform. NH1 had a more typical response at 4000 Hz, but still had a normal response at 250 Hz. At each base, the 25% and 50% modulations were similar to each other, with 50% being more robust, clear, and defined. See Figure 7 for the waveforms of NH1 at 4000 Hz with the 25%(left) and 50%(right) modulations. NH2 had a flat N1 at the 4000 Hz 50% modulation but a more normal N1 at the 250 Hz 50% modulation, which is the opposite of what was expected (see Appendix E).

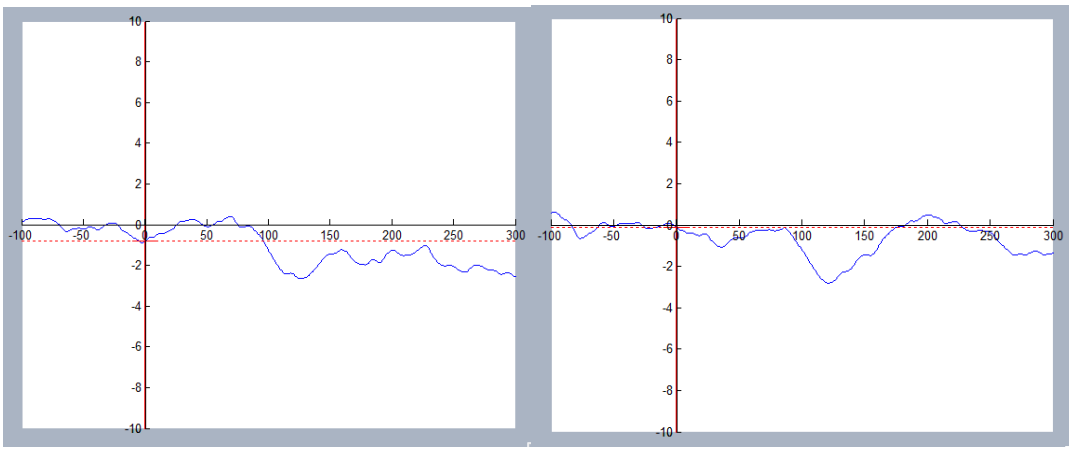


Figure 7: NH1 comparison of 25% and 50% modulation of 4000 Hz

Subject 1 had very low amplitude responses for both 250 Hz and 4000 Hz bases, with the 4000 Hz base block producing larger amplitude. The N1 peak was most noticeable at the 50% modulation on 250 Hz, although it was relatively small (Figure 8). Subject 2 produced extremely varying results, especially with the response waveform at 50% modulation on 4000 Hz (Figure 9). The N1 at this modulation has extremely high amplitude. Subject 3 produced more normal and consistent responses at each condition. The most robust and typical peak occurred at the 50% modulation on 4000 Hz (Figure 10). This subject did present with more normal peaks at the 250 Hz base than the rest of the test group.

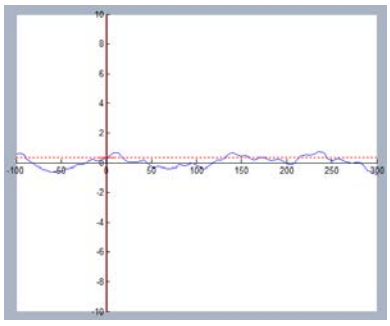


Figure 8: S1 250 Hz 50% mod.

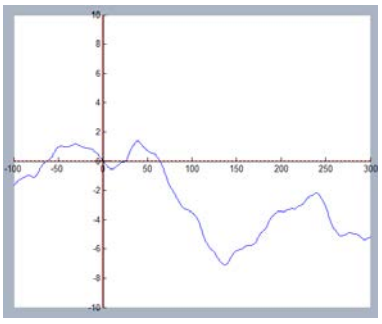


Figure 9: S2 4000 Hz 50% mod.

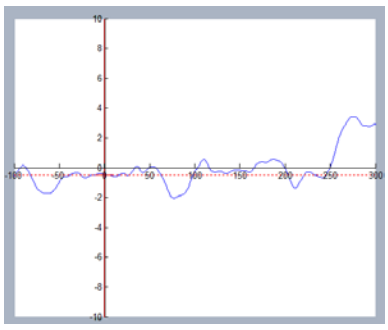


Figure 10: S3 4000 Hz at 50% mod.

3.3 ETIOLOGY OF HEARING LOSS AND BEHAVIORAL DATA

S1 had a large vestibular aqueduct that caused him to develop severe SNHL and receive his CI 5 months prior to testing. According to personal testimony, he is able to use the phone and hear in class in the public school setting but has trouble with the television and distinguishing voices. This is reflected in the record, which says that speech understanding is good when using CI-only. S2 relies on both her CI and hearing aid in order to understand speech. Personal testimony and the audiologic records reflect that she has poor speech recognition when she uses implant-only. S3 received his implant at the youngest age (26 months). Personal testimony and his records indicate that he does very well in his public school setting and has almost no speech difficulty with understanding better than most. He frequently uses implant-only and does not feel he gets much benefit from his hearing aid in his left ear. The participant's behavioral information is in Table 5. MLNT/LNT conditions were monitored live voice at 50 dB HL, lexically easy words.

Table 5: Behavioral Data

Subject	Sound Detection Thresholds	Speech Awareness Thresholds	Speech Recognition Thresholds (Spondee Words)	MLNT	LNT	Behavioral Observations
S1 R ear (CI)	15-20 dB HL		25 dB HL			Understands speech CI alone; Trouble with TV and distinguishing voices
S1 L ear (unaided)			75 dB HL			
S2 R ear (CI)		10 dB HL	35 dB HL	51%		Poor speech recognition with implant
S2 L ear (HA)		10 dB HL	30 dB HL	91%		
S3 R ear (CI)		0 dB HL	25 dB HL		monitored live: 96%; recorded: 76%	Speech understanding considered "better than most"; not often wear HA

4.0 DISCUSSION

The goal of this study was to learn the methodology for extracting the artifact produced by a CI during the recording of a cortical evoked potential in children. Cortical responses were recorded from three children with unilateral CIs in response to two continuous pure tones of 250 Hz and 4000 Hz modulated at depths from 0% to 50%. Two children wore a hearing aid on the ear opposite the CI. CAEPs were obtained from all 3 of the children and from 2 normal-hearing young adults. Waveform morphologies across the 3 implanted children were highly variable, but removal of the CI artifact had its greatest effect on the earliest components of the evoked responses and did not appear to alter the P1-N1-P2 complex of primary interest to the study.

4.1 ARTIFACT REJECTION

An artifact presumably produced by each child's CI was identified in the ongoing EEG obtained in response to the auditory stimuli. The waveform of the artifact was variable from person-to-person. Typically, within each individual, the artifact appeared as a consistent waveform across the two frequency conditions of 250 Hz and 4000 Hz. It is possible that the artifact identified through the ICA process may differ across types of implant. None of the subjects had the same model of implant, although S1 and S3 had the same brand. The components identified in the responses obtained from S1 and S3 were more similar than between S1 and S2 or S3 and S2, but

not as similar as between the conditions within a single subject. The ICA method for identifying the CI artifact in this study appeared to be reasonably successful at removing an early component with a similar morphology to the artifact reported earlier (Gilley et al., 2007). In previous studies, however, the auditory stimulus was brief, resulting in a definitive onset and offset of the implant processor in response. In this study, the frequency modulations occurred against the background of a continuous pure tone, so it was possible that the implant artifact may have extended across the full recording epoch. Efforts were made to determine if that was the case, but removal of artifacts with latencies in the region of the P1-N1-P2 response did little to alter the morphology of the overall response, so it was unclear whether the use of a continuous tone changed the nature of the ICA process for artifact identification. In this study, the onset of the frequency modulation was used to trigger the evoked response, so it was presumed that the artifact from the CI that occurred immediately after the stimulus changed was the primary artifact of interest. Results from this analysis would suggest that the use of an ongoing stimulus, particularly a base pure tone, does not produce an additional artifact that needs to be removed from the overall evoked response.

4.2 CAEPS AND BEHAVIORAL DATA

It was expected that the CAEP responses would vary from subject to subject, but the relatively high degree of variation across these three children was surprising. In all 3 of the children, the 50% modulation on both base frequencies produced the maximal response. Whether this indicates that the 50% modulation has a higher degree of discrimination ability in this population is not clear from this study, but is a potential hypothesis for future research. The N1 response to

modulations of the 4000 Hz pure tone was generally more robust than the response to modulations of the 250 Hz pure tone. Interestingly, one of the normal-hearing participants produced a response with a larger amplitude at 250 Hz than at 4000 Hz (NH2). Despite this, it appears that the cortical evoked response to frequency modulations on a 4000 Hz pure tone might be useful as a potential index of discrimination or attention to rapid alterations in an ongoing auditory stimulus in this population. As mentioned earlier, this could potentially be related to greater ability to process the temporal fine structure used to differentiate among normally occurring speech sounds (Lorezni et al., 2006). The finding of a more robust N1 response with modulations to the 4000 Hz base is also consistent with previous research by Dimitrijevic and colleagues (2011).

The occasional incidence of a large P3-like component may have been related to the participant being allowed to play a game. This may have also affected the total number of eye blinks that the participant produced, because with each CI participant who was allowed to play a game during the study, there was an abnormally low amount of blinks present in the data. It is possible that focusing the eyes downward at a screen while playing a game limits the overall excursion of the eyelid during normal blinking, thereby reducing the number of eye blinks that need to be removed from the ongoing EEG (Moncrieff, personal communication).

Since there is such a large range of frequencies between 250 Hz and 4000 Hz, future studies should explore the cortical response to pure tones of 1000 Hz or 2000 Hz modulated at similar depths since those frequencies are so vital to normal speech discrimination.

For comparison, the data from the 50% modulations for each condition for each participant is presented in Figure 11. The arrows indicate which peaks were identified as the P1

(red), N1 (blue) and P2 (green) in this study. If there is no arrow, it implies that the peaks were unclear.

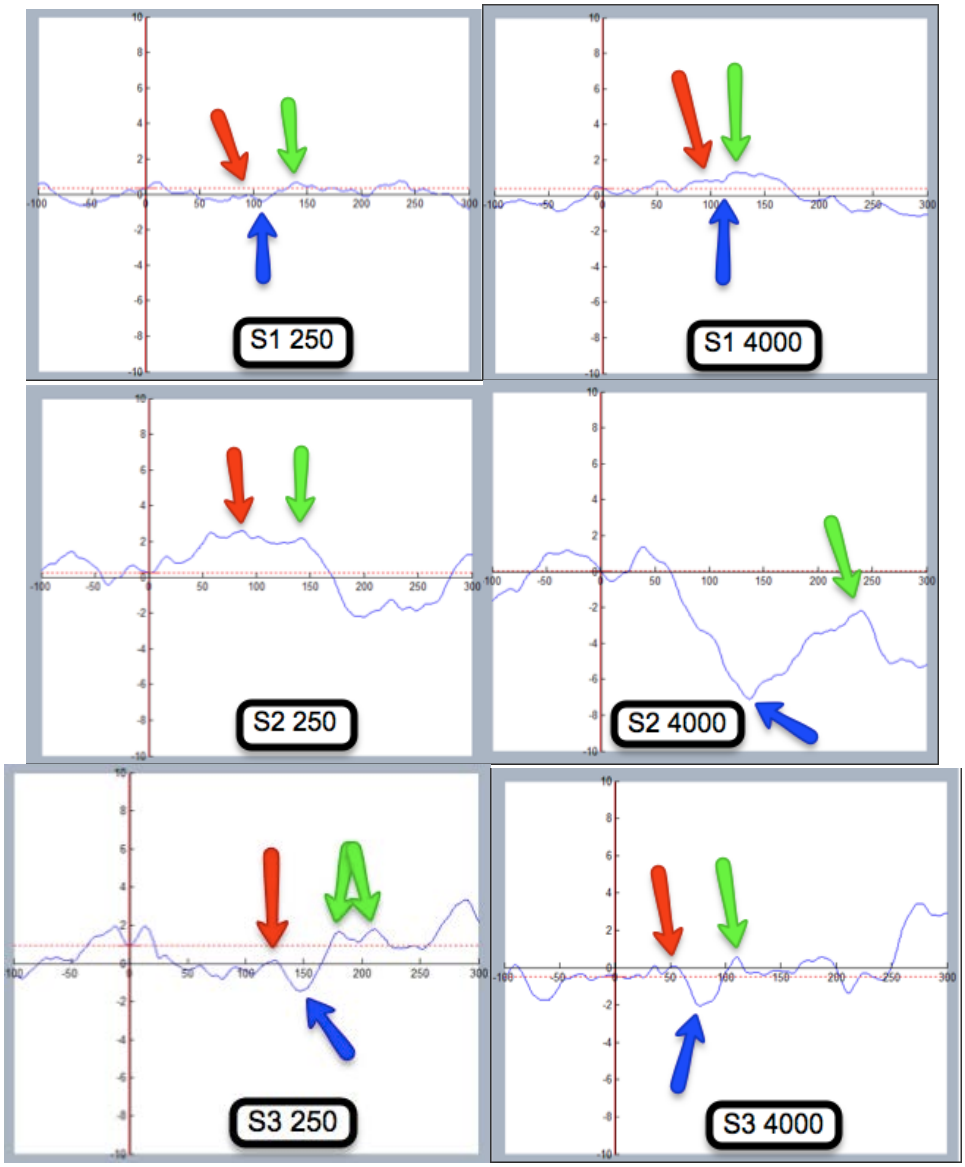


Figure 11: 50% Modulation with Peak Identification

As mentioned above and can be seen in the above figure, the resulting waveforms are highly variable for each subject. S1 has peaks with very small amplitude that are difficult to discern. S2 has what appears to be a very large N1. S3 has a small but measurable N1, with peaks that seem the most typical of this test group.

With so limited a study, definitive conclusions cannot be made, but individual differences across these children may have contributed to the dramatic variability in their response morphologies. S1 may have low amplitude responses because he has had a short time since implantation (5 months) or because of his etiology (vestibular aqueduct). This could potentially be related to the behavioral report that he has difficulty differentiating people's voices when they are speaking. With more time with continuous auditory stimulation through the implant, the N1 may appear in the evoked response with peaks occurring at a normal amplitude. It is possible that the data for S2 (with a very large N1) appears different than the other two because she is left-handed but has a right cochlear implant. It is likely that hemispheric lateralization for language in these children varies as it does in the normal population and whether side of implant interacts with side of hemispheric dominance could be investigated. More patients of this same feature should be tested to make that determination. S2 has a score on the MLNT of 51% of lexically easy words correct. This data can be compared with S3, who has a higher score on the LNT, which is also a more difficult test. Since her results are more abnormal than S3, there is potential that the scores on this test correlate to the amplitudes and latencies of the P1-N1-P2 complex. Although the amplitudes for S3 were small, he has the most typical waveform of the three participants. This could be related to his behavioral results, since he was said to do 'better than most' with his CI, and does not feel the need to use a hearing aid. Behavioral correlations would need to be evaluated in the context of a larger study. It is interesting to note that S3 used implant-only and appeared to have the most normal of the responses. This could mean that his performance is more like a normal-hearing person because he does so well with his implant and/or because he does not use his hearing aid, the response is only a reflection of processing by one side, and is therefore easier to evaluate. The results from S3 point to another possibility for

future study. If you were to plug and muff the non-implant ear, the response could potentially be investigated to determine that it was implant-only. An issue with this type of study is that there would be a loss of real-life validity.

5.0 CONCLUSION

This study was primarily designed to explore the methodologies required to successfully record CAEPs from children with cochlear implants. In all three of the CI children tested in this study, an independent component most likely related to the artifact produced by the cochlear implant was identified and extracted from the ongoing waveform of the CAEP. Measurement of CAEPs in children with CIs opens numerous opportunities for objective evaluation of the auditory pathway in these patients. This method can be used to assess the auditory pathway pre- and post-implant and may ultimately provide important information about the effects of auditory deprivation, the limits and benefits of implantation, and the individual factors that may affect successful use of a cochlear implant in a child. In a larger population of CI recipients, it may be feasible to compare objective electrophysiologic measures to ongoing behavioral outcomes. Evidence of neurophysiologic activity in the auditory system could be useful in planning and modifying management strategies for children with cochlear implants and may ultimately serve to predict outcomes across individual patients prior to implantation.

APPENDIX A

RECRUITMENT PHONE SCRIPT

"When you bring your child into Forbes Tower on the day of testing, we will have you review and sign the consent form and ensure all of your questions are answered. We will place one of our stretchy caps on your child's head, ensuring that it fits comfortably. This cap looks like a bathing cap that has wires attached to electrodes that pick up tiny electrical signals. These signals are always there; your child cannot and will not feel them or the recording of them. To pick up these invisible signals, we need to place a gel into holes in the cap that will reach to the child's head. This is the only part that the child will feel. The gel will feel cool but will not hurt your child. We will then play tones through a loudspeaker while he/she sits still and quiet. If your child will be too bored, he/she could potentially look at a book or movie turned on silent during the time these tones are played. We will then remove the cap and if your child is comfortable, the gel can be washed out of his/her head in the sink in the laboratory. You can also choose to do this at home, as the gel will not cause harmful affects to your child's head or hair. It is salt-based and dissolves in water. The entirety of your visit should be about two hours."

APPENDIX B

WAVEFORM ANALYSIS CHECKLIST

Waveform Analysis Checklist
Subject Number: _____
Stimulus: _____250 Hz _____4000 Hz

In Stim Edit:									
Epoch File to Ident. Bad Elec.	Remove Bad Electrodes	Identify and Mark HEO Peaks	Average HEO Marks	Spatial SVD	Linear Derivation	Spatial Filter	Decimate	Modify Redundants	Create Event File
In Matlab:			Import DCM MOD file	Import Event File	Add Channel Locations	Create ERP Eventlist	Extract Bin-Based Epochs	Run ICA	
Rejection in Matlab:		Aquire Pre-Rej Waveform	Evaluate Large Components	Identify Components	Record Component Statistics	Remove Components	Filter Waveform	Compute Average ERP	Evaluate Waveform

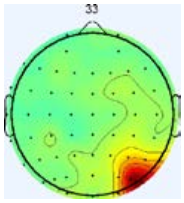
APPENDIX C

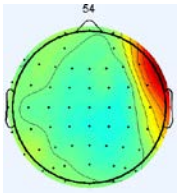
REJECTION DATA

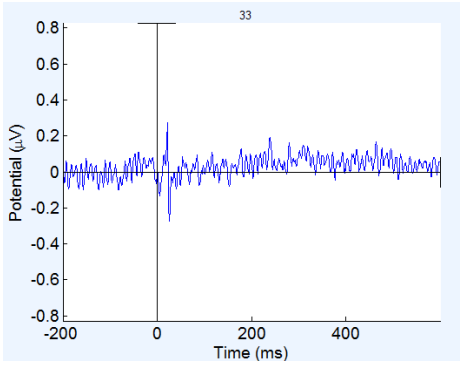
Following are independent component waveforms with head plots that were rejected from further analysis, in addition to examples of components that were considered, but not rejected from the data.

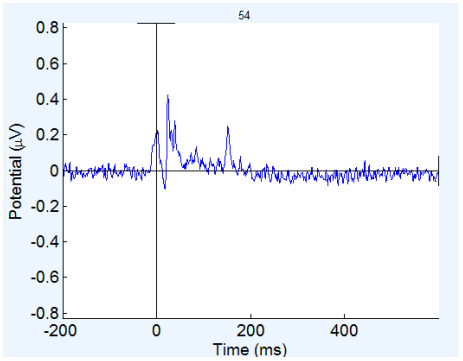
C.1 REJECTED COMPONENTS

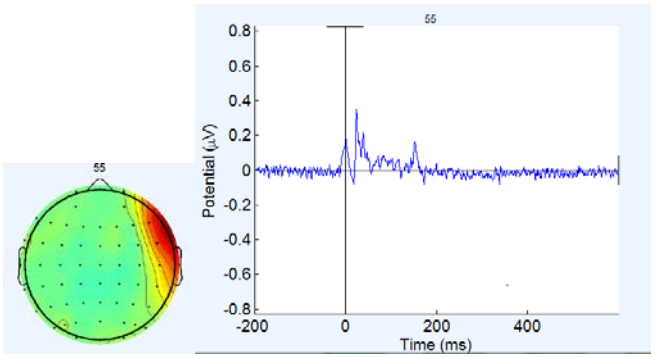
S1 250 Hz:



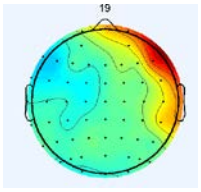


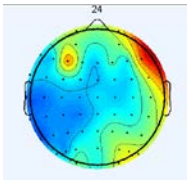

33
Potential (μV)
Time (ms)

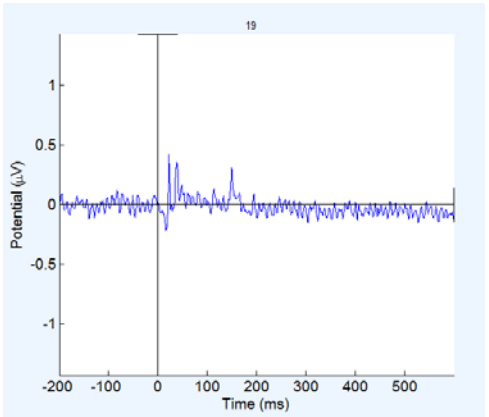

54
Potential (μV)
Time (ms)

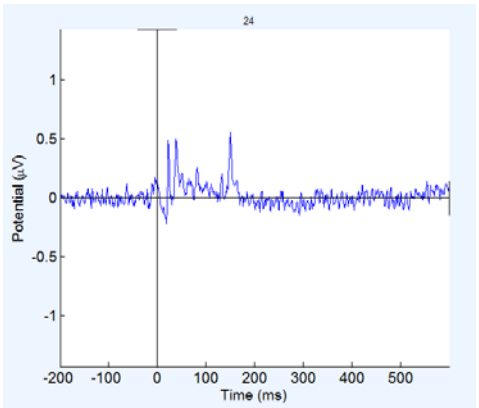

55
55
Potential (μV)
Time (ms)

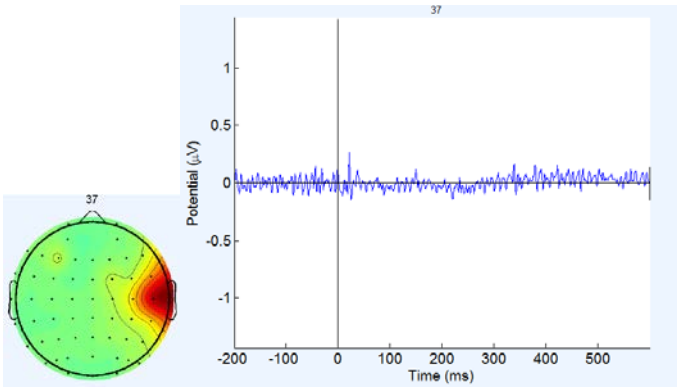
S1 4000 Hz:


19

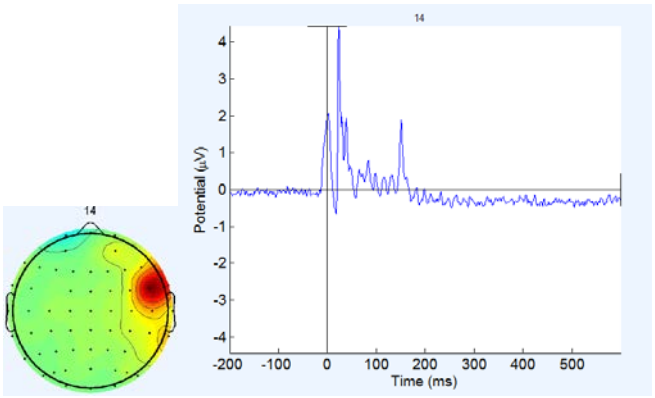

24


19
Potential (μV)
Time (ms)

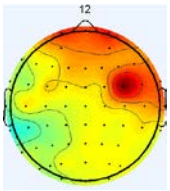

24
Potential (μV)
Time (ms)

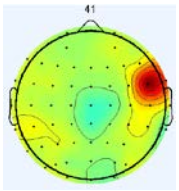


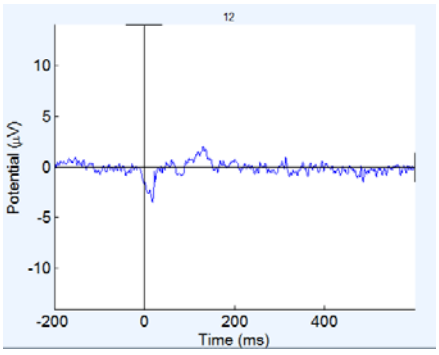
S2 250 Hz:

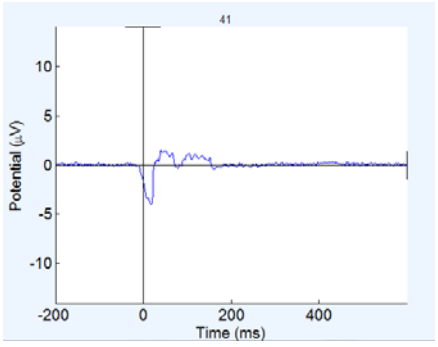


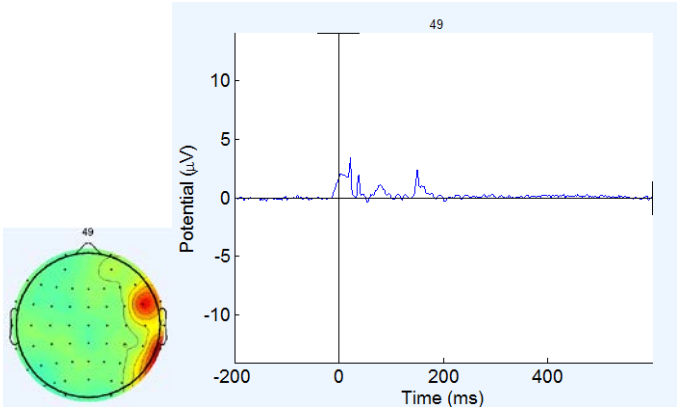
S2 4000 Hz



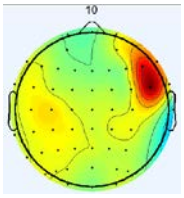


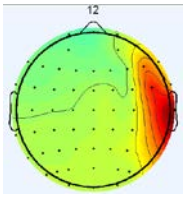


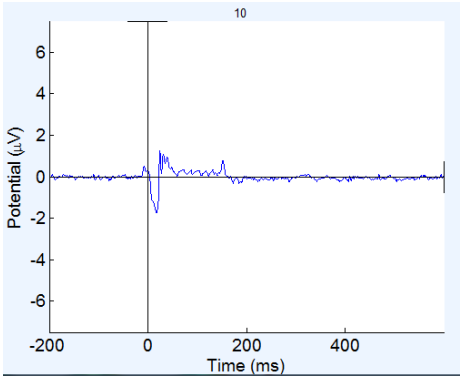


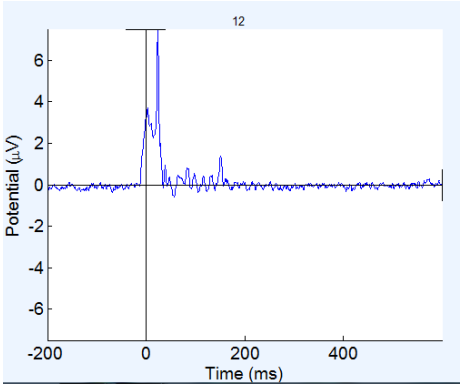


S3 250 Hz:

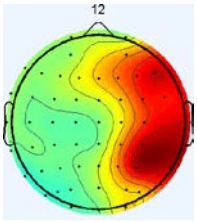


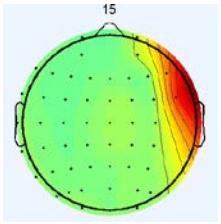


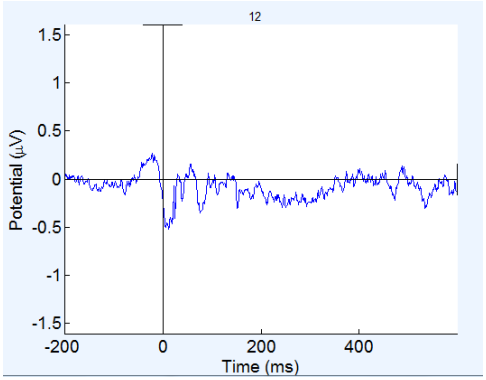


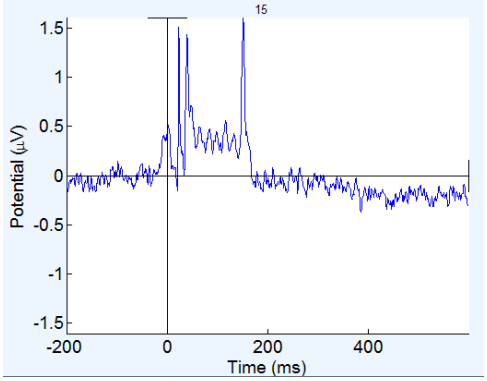


S3 4000 Hz:







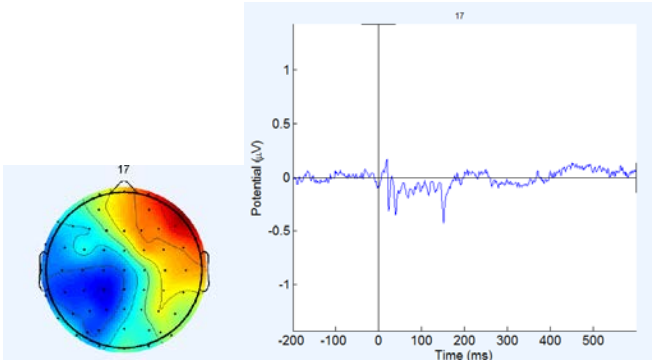


C.2 REJECTED COMPONENT STATISTICS

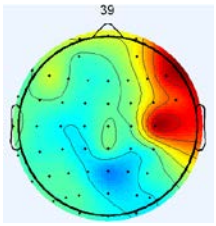
Subject	Comp. #	Standard Dev.	Variance	Range	Skewness	Excess Kurtosis	Distribution
S1 250	33	1.22	1.42	15.04	-0.12	1.41	super-Gaussian
	54	0.53	0.28	5.03	0.01	0.03	super-Gaussian
	55	0.45	0.2	4.31	0.02	0.03	super-Gaussian
S1 4000	19	1.67	2.8	25.87	-0.41	2.91	super-Gaussian
	24	1.27	1.62	21.42	0.4	3.34	super-Gaussian
	37	1.09	1.19	103.7	0.37	244	super-Gaussian
S2 250	14	2.85	8.1	23.93	-0.004	0.99	super-Gaussian
S2 4000	12	15.49	239.8	519	-0.42	5.91	super-Gaussian
	41	3.73	13.89	38.61	-0.02	0.76	super-Gaussian
	49	2.79	7.78	27.63	0.18	0.78	super-Gaussian
S3 250	10	3.39	11.52	47.35	-0.13	2.12	super-Gaussian
	12	3.14	9.87	43.93	0.11	0.94	super-Gaussian
S3 4000	12	3.16	9.96	50.85	-0.34	3.7	super-Gaussian
	15	2.71	7.34	25.61	0.09	1.04	super-Gaussian

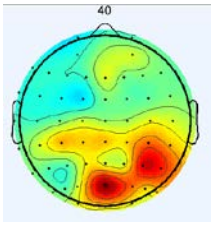
C.3 RETAINED COMPONENTS

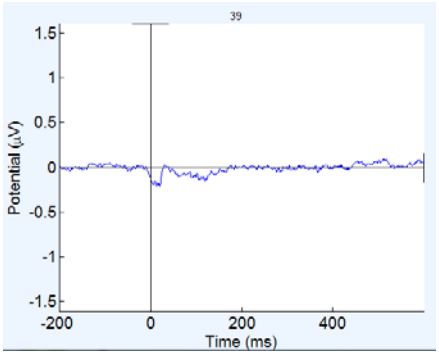
The following component was retained because of the large negative potential around 180ms.

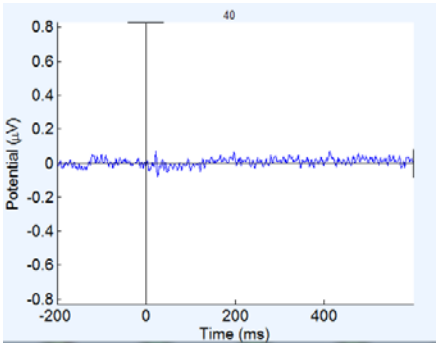


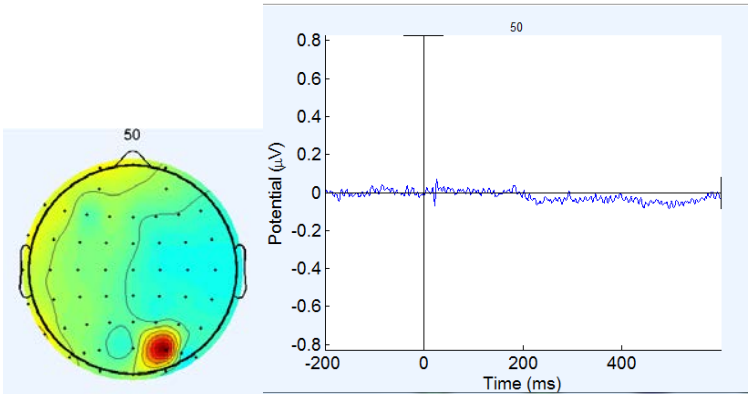
The following components were retained because of their small relative variance.









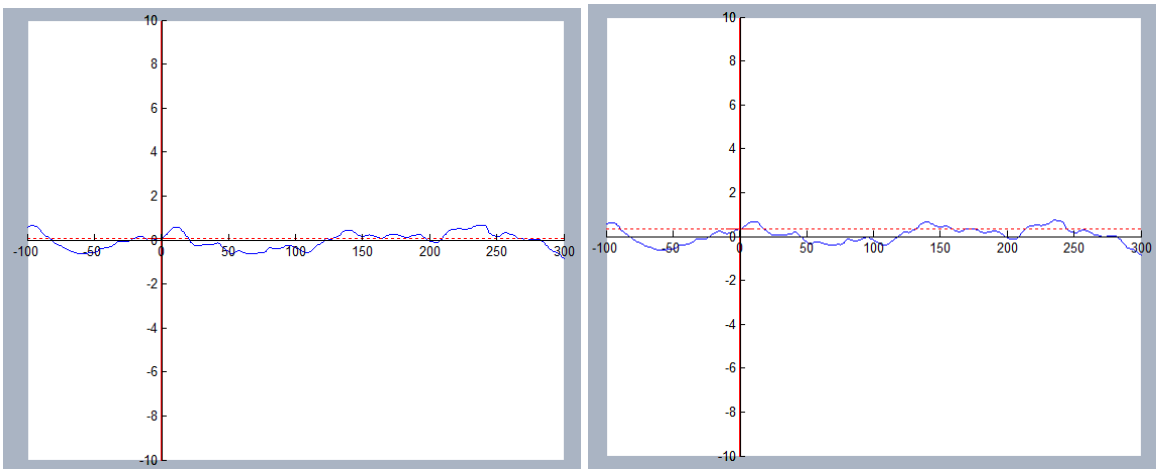


APPENDIX D

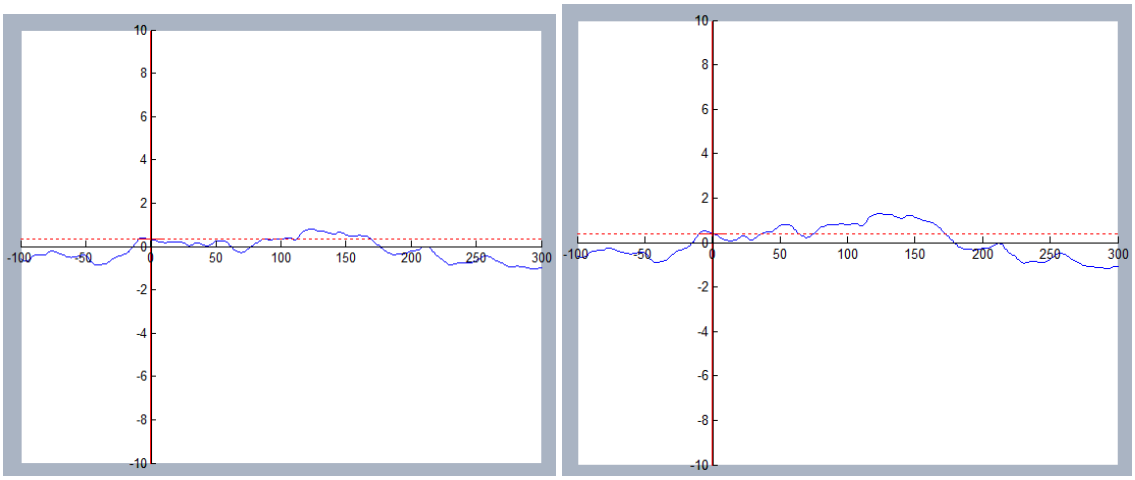
PRE AND POST REJECTION WAVEFORMS

Following are the waveforms for each stimulus at the 50% modulation verifying that the rejection of the cochlear implant artifact has been successful: the components of interest were removed. The change was often only in small intervals. Pre-rejection is on the left and post-rejection is on the right.

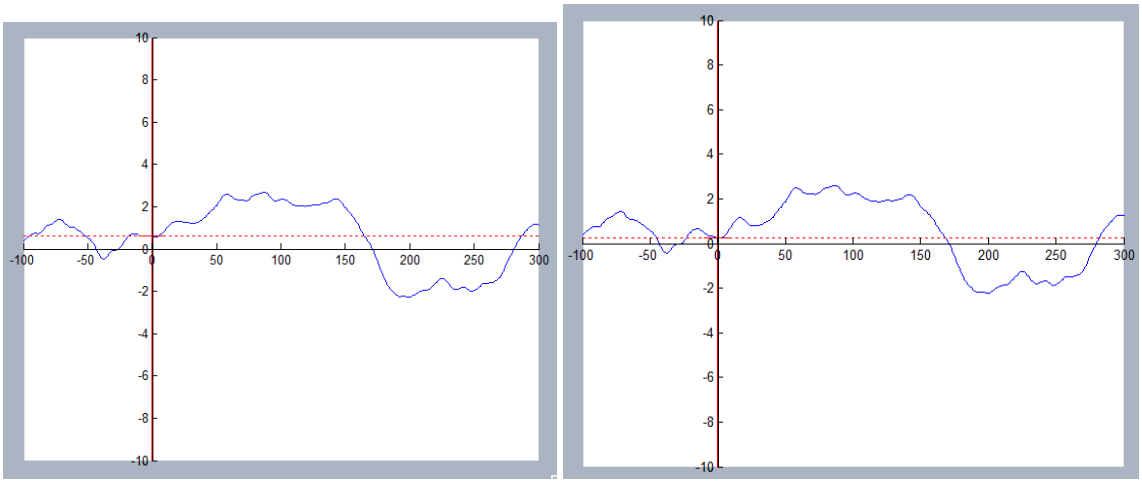
S1 250 Hz



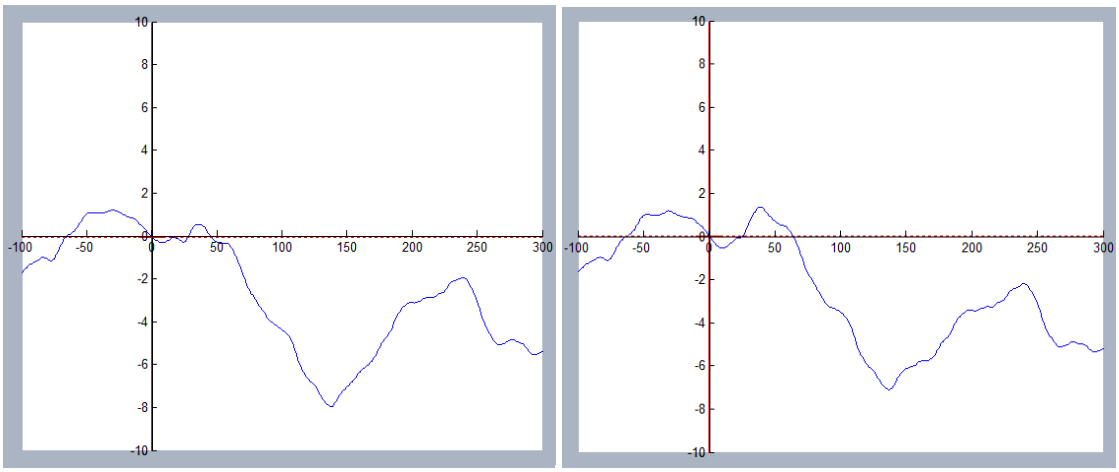
S1 4000 Hz



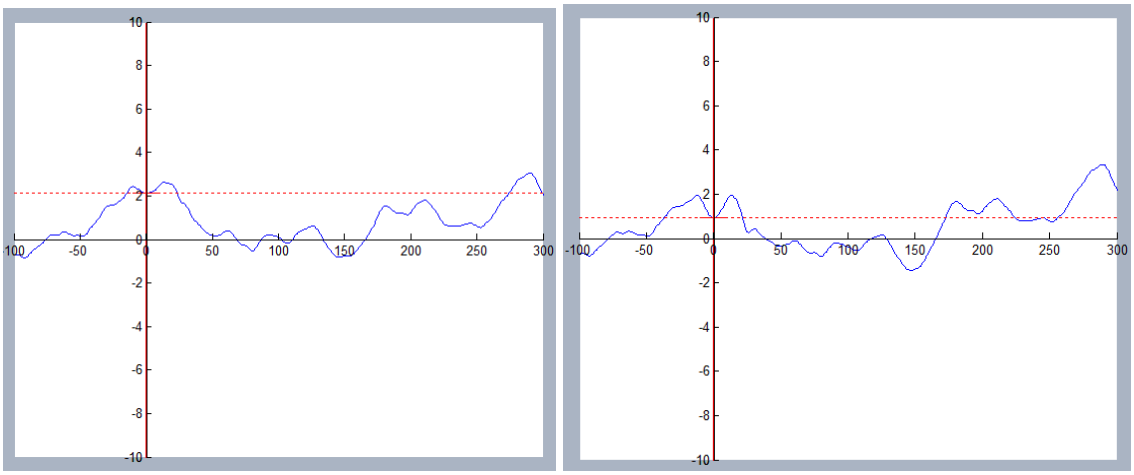
S2 250 Hz



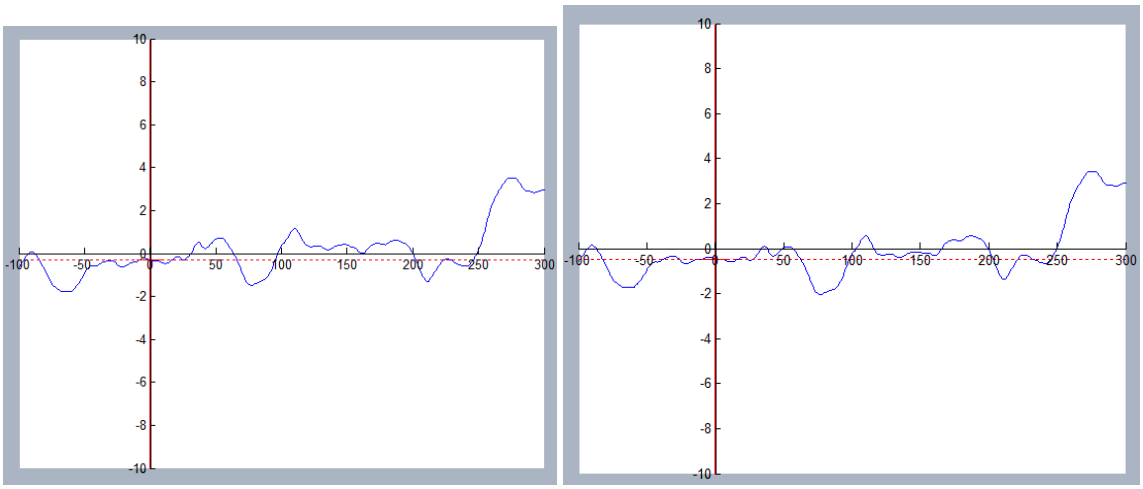
S2 4000 Hz



S3 250 Hz



S3 4000 Hz

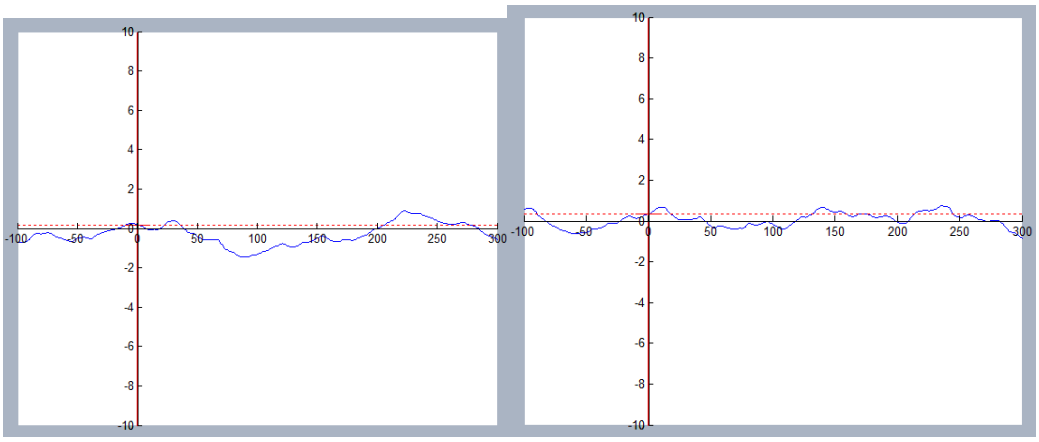


APPENDIX E

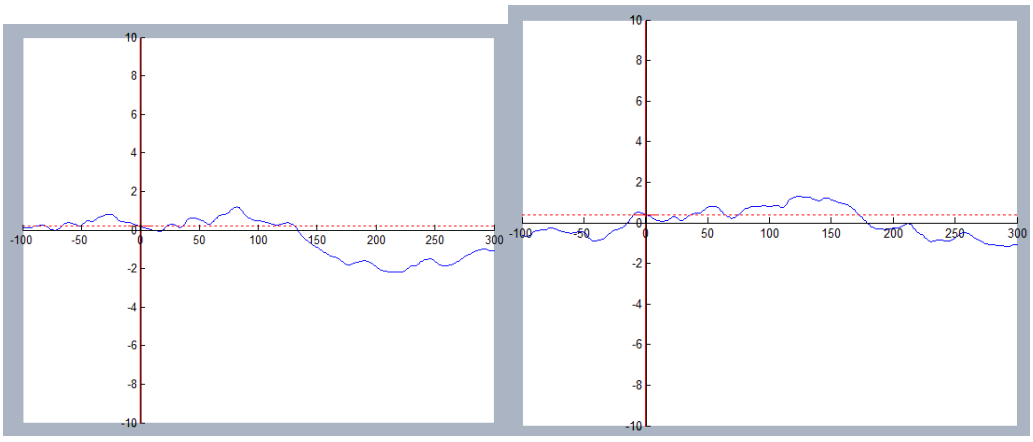
RESULTING WAVEFORMS

The resulting waveforms for each participant at the frequency modulations of 25% (left) and 50% (right) for each base for the subjects (S1, S2, S3) and normals (NH1, NH2). Baseline is red.

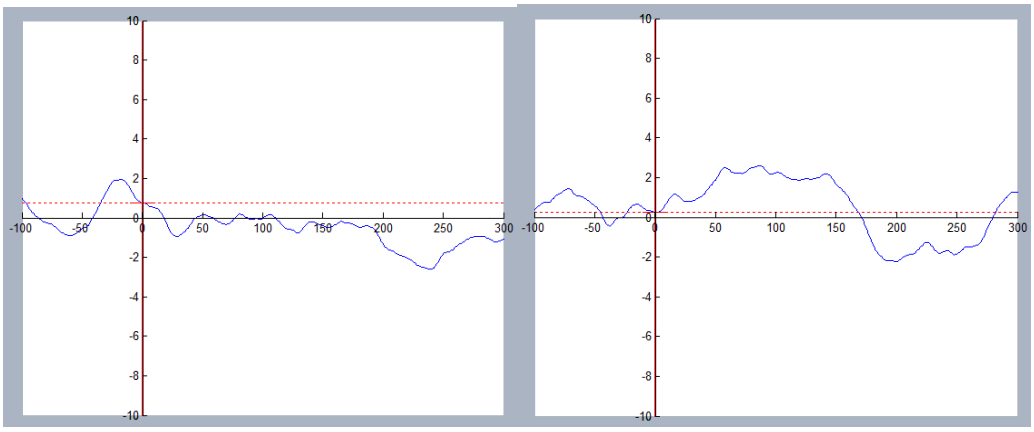
S1 250 Hz



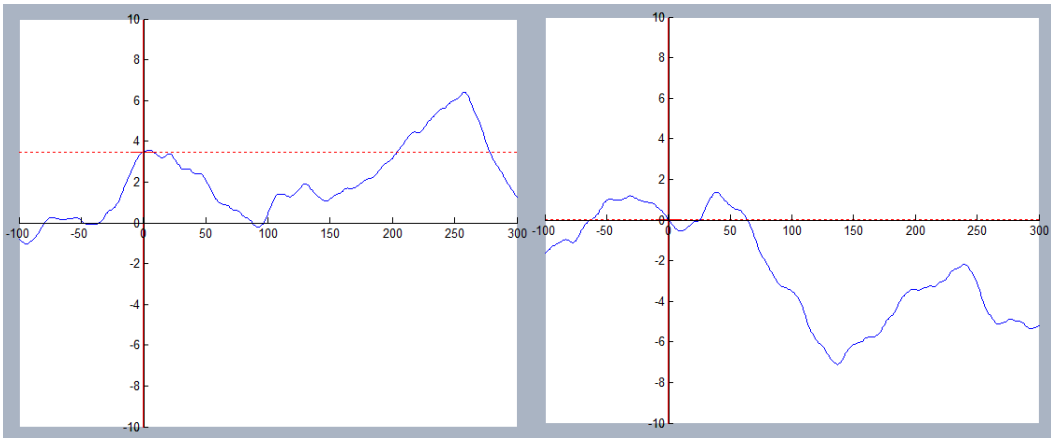
S1 4000 Hz



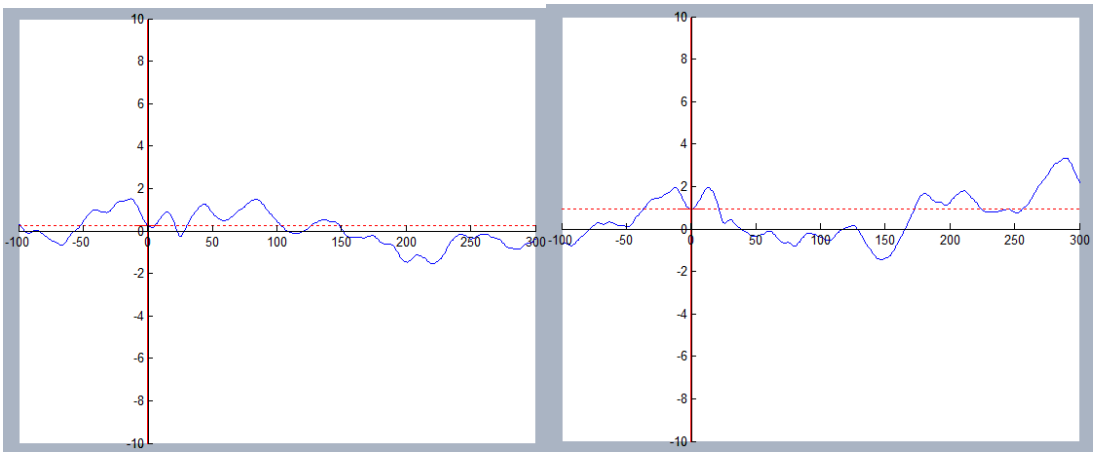
S2 250 Hz



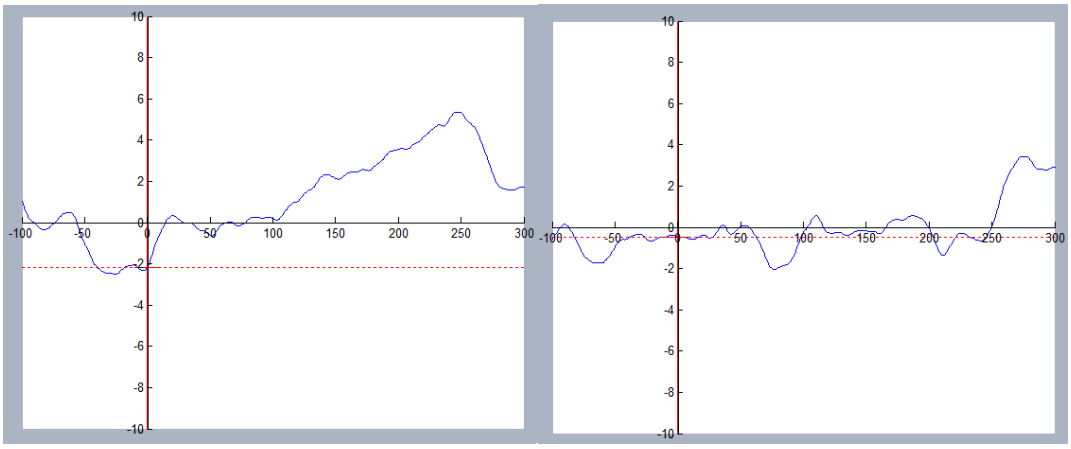
S2 4000 Hz



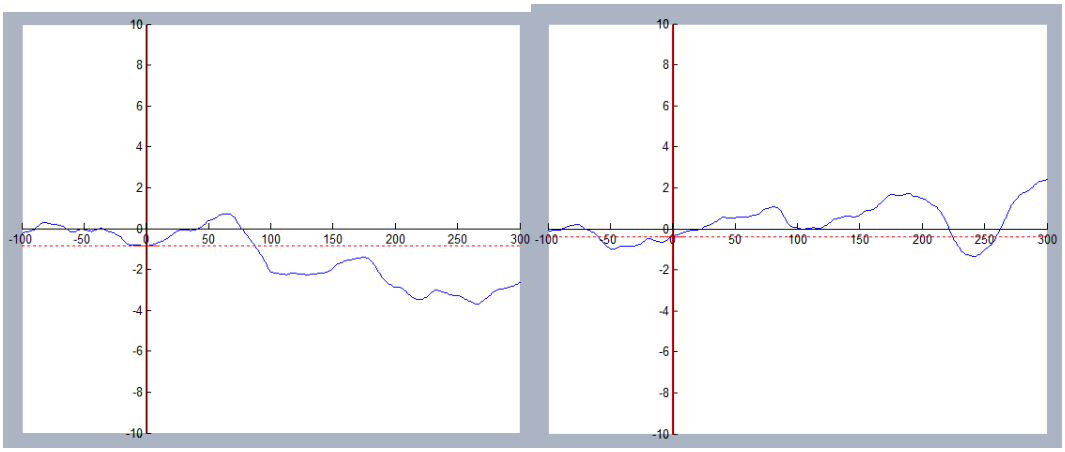
S3 250 Hz



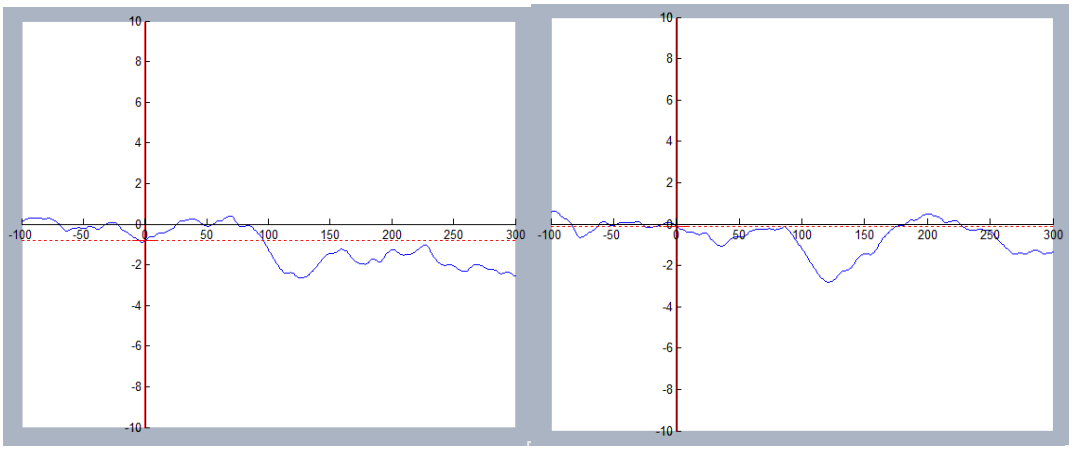
S3 4000 Hz



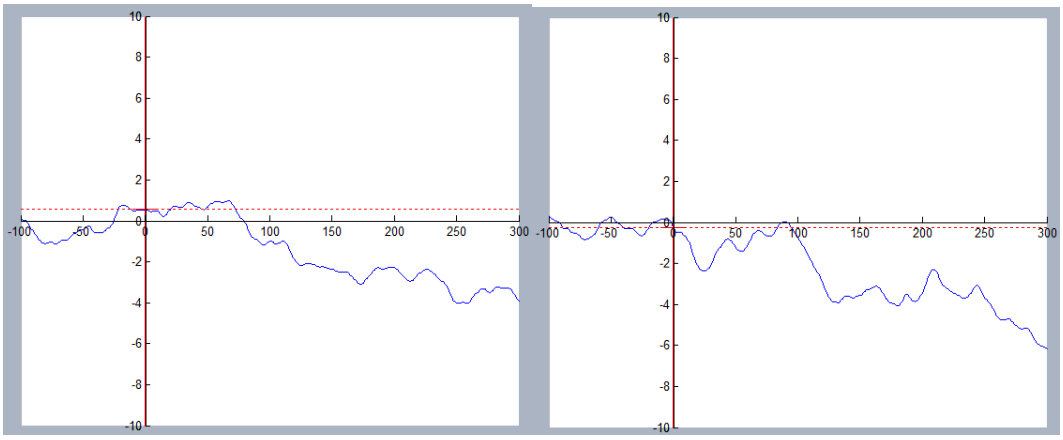
NH1 250 Hz



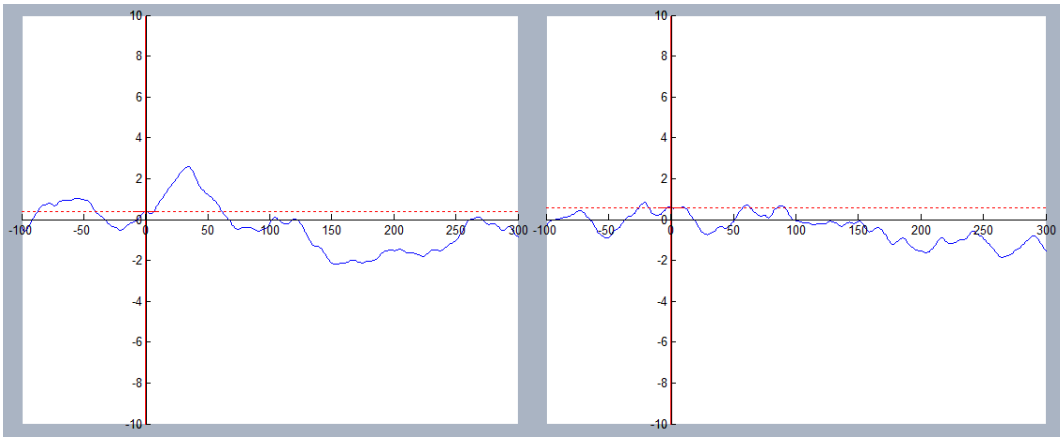
NH1 4000 Hz



NH2 250 Hz



NH2 4000 Hz



REFERENCES

American Speech-Language-Hearing Association. (2004). *Cochlear implants* [Technical Report]. Available from www.asha.org/policy. doi:10.1044/policy.TR2004-00041

Bell, A.J., & Sejnowski, T.T. (1995). An information-maximization approach to blind separation and blind deconvolution. *Journal of Computational Neuroscience*, *7*(6), 1129-1159.

Berlin, C.I., Hood, L.J., Morlet, T. Wilensky, D., Li1, L., Mattingly, K.R., Taylor-Jeanfreau, J., Keats, B.J.B., St. John, P., Montgomery, E., Shallop, J.K., Russell, B.A., & Frisch, S.A. (2010). Multi-site diagnosis and management of 260 patients with auditory neuropathy/ dys-synchrony (auditory neuropathy spectrum disorder*). *International Journal of Audiology*. *49*, 30-43. doi: 10.3109/14992020903160892

Burkard, R.F., Don, M., & Eggermont, J.J. (2007). *Auditory evoked potentials basic principles and clinical application*. Baltimore, MD: Lippincott Williams & Wilkins.

Caldwell, A. & Nittrouer, S. (2013). Speech perception in noise by children with cochlear implants. *Journal of Speech, Language, and Hearing Research, 56*, 13-30.

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-tril EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*, 9-21. doi:10.1016.j.jneumeth.2003.10.009.

Dimitrijevic, A., Michalewski, H.J., Zeng, F.G., Pratt, H., Starr, A. (2008). Frequency chances in a continuous tone: Auditory cortical potentials. *Clinical Neurophysiology*, *119*, 211-2124. doi:10.1016/j.clinph.2008.06.002

Dimitrijevic, A., Starr, A., Bhatt, S., Michalewski, H.J. Zeng, F., Pratt, H. (2011). Auditory cortical N100 in pre- and post-synaptic auditory neuropathy to frequency or intensity changes of continuous tones. *Clinical Neurophysiology*, *122*, 594-604. doi:10.1016/j.clinph.2010.08.005

Dorman, M.F., Sharma, A., Gilley, P., Marin, K., & Roland, P. (2007). Central auditory development: Evidence from CAEP measurements in children fit with cochlear implants. *Journal of Communication Disorders, 40*(4), 284-294. doi:10.1016/j.jcomdis.2007.03.007.

Edwards L.C., Frost, R., Witham, F. (2006). Developmental delay and outcomes in paediatric cochlear implantation: Implications for candidacy. *International Journal of Pediatirc Otorhinolaryngology*, *70*, 1593-1600. doi:10.1016/j.ijporl.2006.04.008.

Eggermont, J.J., & Ponton, C.W. (2002). The neurophysiology of auditory perception: From single units to evoked potentials. *Audiology & Neuro-Otology*, *7*, 71-99.

Eggermont, J.J., & Ponton, C.W. (2003). Auditory-evoked potential studies of cortical maturation in normal hearing and implanted children: correlations with changes in structure and speech perception. *Acta Oto-Laryngologica*, *123*, 249-252. doi:10.1080/0036554021000028098.

Ertmer, D.J., Goffman, L. (2011). Speech production accuracy and variability in young cochlear implant recipients: Comparisons with typically developing age-peers. *Journal of Speech, Language, and Hearing Research*, *54*, 177-189.

Gilley, P.M., Sharma, A., & Dorman, M.F. (2008). Cortical reorganization in children with cochlear implants. *Brain Research, 1239,* 56-65. doi:10.1016/j.brainres.2008.08.026

Gilley, P.M., Sharma, A., Dorman, M., Finley, C.C., Panch, A.S., & Martin, K. (2006). Minimization of cochlear implant stimulus artifact in cortical auditory evoked potentials. *Clinical Neurophysiology*, 117, 1772-1782. doi:10.1016/j.clinph.2006.04.018.

Greenberg, J.H., & Jenkins, J. J. (1964). Studies in the psycho- logical correlates of the sound system of American English. *Word, 20,*157-177.

Hayes, D. (2011). A brief review of aetiologies associated with auditory neuropathy. *ENT & audiology news*, *19*(6), 73-74.

Hyde, M., Punch, R., & Komesaroff, L. (2010). A comparison of the anticipated benefits and received outcomes of pediatric cochlear implantation: Parental perspectives. *American Annals of the Deaf*, *155*(3), 322-338).

Jeong, S., Kim, L., Kim, B., Bae, W., & Kim, J. (2007). Cochlear implantation in children with auditory neuropathy: Outcomes and rationale. *Acta Oto-Laryngologica*, *Suppl 558*, 36-43. doi:10.1080/03655230701624848

Kirk, K.I., Pisoni, D.B., Osberger, M.J. (1995). Lexical effects on spoken word recognition by pediatric cochlear implant users. *Ear & Hearing*, 16(5), 470-481.

Kumar, U.A., Jayaram, M.M. (2006). Prevalence and audiological characteristics in individuals with auditory neuropathy/auditory dys-synchrony. *International Journal of Audiology*, 45, 360-366. doi:10.1080.14992020600624893

Kumar, U.A., Jayaram, M.M. (2005). Auditory processing in individuals with auditory neuropathy. *Behavioral and Brain Functions*, *1*(21). doi:10.1186/1744-9081-1-21

Lin, F.R., Wang, N., Fink, N.E., Quittner, A.L., Eisenberg, L.S., Tobey, E.A., Niparko, J.K., & CDaCI Investigative Team. (2008). Assessing the use of speech and language measures in relation to parental perceptions of development after early cochlear implantation. *Otology & Neurotology*, *29*(2), 208-213.

Lorenzi, C., Gilbert, G., Carn, H., Garnier, S., & Moore, B.C.J. (2006). Speech perception problems of the hearing impaired reflect inability to use temporal fine structure. *Proceedings of the National Academy of Sciences of the United States of America, 103*(49), 18866-18869.

Luce, P. (1986). *Neighborhoods of words in the mental lexicon* (Research on Speech Perception Technical Report No. 6). Bloomington, IN: Speech Research Laboratory, Indiana University.

Luce, P. A., Pisoni, D. B., & Goldinger, S. D. (1990). Similarity neighborhoods of spoken words. In G. T. M. Altmann (Ed.), *Cognitive models of speech processing: Psycholinguistic and computational perspectives.* Cambridge, MA: MIT Press.

Luck, S., & Lopez-Calderon, J. (2012). ERPLAB toolbox version 3.0. http://erpinfo.org/erplab

Marco, J., Morant, A., Orts, M., Pitarch, M.I., & Garcia, J. (2000). Auditory neuropathy in children. *Acta Otolaryngol*, *120*, 201-204.

McPherson, D.L. (1996). *Late Potentials of the Auditory System.* San Diego, California: Singular Publishing Group.

Niparko, J.K, & Blankenhorn, R. (2003). Cochlear implants in young children. *Mental Retardation and Developmental Disabilities Research Reviews*, *9*, 267-275.

Ponton, C.W., Don, M., Eggermont, J.J., Waring, M.D., Kwong, B., & Masuda, A. (1996). Auditory system plasticity in children after long periods of complete deafness. *NeuroReport*, *8*(1), 61-65.

Ponton, C.W., Eggermont, J.J., Kwong, B., & Don, M. (2000). Maturation of human central auditory system activity: Evidence from multi-channel evoked potentials. *Clinical Neurophysiology*, *111*, 220-236.

Rance, G., & Barker, E. (2009). Speech and language outcomes in children with auditory neuropathy/dys-synchrony managed with either cochlear implants or hearing aids. *International Journal of Audiology*, *48*(6), 313-320. doi:10.1080/14992020802665959

Sininger, Y. (2011). An introduction to auditory neuropathy spectrum disorder. *ENT & audiology news*, *19*(6), 70-71.

Sininger, Y.S., & Trautwein, P. (2002). Electrical stimulation of the auditory nerve via cochlear implants in patients with auditory neuropathy. *Annals of Otology, Rhinology, & Laryngology*, *111*, 29-31.

Sharma, A., Cardon, G., Henion, K., & Roland, P. (2011). Cortical maturation and behavioral outcomes in children with auditory neuropathy spectrum disorder. *International Journal of Audiology, 50*, 98-106.

Sharma, A., Dorman, M., & Spahr, A.J. (2002). A sensitive period for the development of the central auditory system in children with cochlear implants: Implications for age of implantation. *Ear & Hearing, 23*(6), 532-539. doi:10.1097/01.AUD.0000042223.62381.01.

Sharma, A., Nash, A.A., & Dorman, M. (2009). Cortical development, plasticity and re-organization in children with cochlear implants. *Journal of Communication Disorders, 42*(4), 272-279. doi:10.1016/j.jcomdis.2009.03.003.

Starr A., Picton, T.W., & Kim, R. (2001). Pathophysiology of auditory neuropathy. *Auditory Neuropathy: A New Perspective on Hearing Disorders*. San Diego, CA: Singular. 67-82.

Van Dijk, J.E., Van Olphen, A.F., Langereis, M.C., Mens, L.H.M., Brokx, J.P.L., & Smoorenburg, G.F. (1999). Predictors of cochlear implant performance. *Audiology*, 38, 109-116.

Wie, O.B., Falkenberg, E., Tvege, O., & Tomblin, B. (2007). Children with a cochlear implant: Characteristics and determinants of speech recognition, speech-recognition growth rate, and speech production. *International Journal of Audiology*, *46*, 232-243. doi:10.1080/14992020601182891

Zeng, F.G. & Liu, S. (2006). Speech perception in individuals with auditory neuropathy. *Journal of Speech, Language, and Hearing Research*, *49*, 367-380.